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THE POSITION OF CAESAREAN SECTION IN DENMARK

By PER SCHOU

The position of Caesarean section (C. s.) in obstetrics has been the object of repeated discussion during the most recent years. Lately, C. s. was thus the main topic at two congresses of gynaecology and obstetrics, viz. in London in 1949 and in Copenhagen in 1952.

On the latter occasion, the author in co-operation with E. Brandstrup (3) presented a review of Danish experience of delivery with C. s. over a period of 10 years.

In the present paper an attempt has been made to give a more detailed analysis of the incidence, indications and prognosis of the operative method of delivery, both within the various medical districts of this country and in Denmark in its entirety. The results of the analysis will be compared with accounts available from abroad.

While by far the majority of the papers concerning C. s. contributed from abroad concentrate on statistics from single departments this investigation has taken advantage of the relatively small size of Denmark to include the whole country.

Our material, which thus comprises all the abdominal C. s. performed in Denmark during a ten-year period 1941—1950, is based upon the annual reports to the National Health Service from all hospitals and hospital departments throughout the country, supplemented by personal communication with the hospitals concerned, where this was necessary.

It will be observed in the following that in recording the material the ten-year period has been divided into two halves, thereby making it possible to compare the conditions in two five-year periods prior to and after the commencement of 1946, a date, which corresponds approximately to the effective introduction of penicillin into clinical use in this country.

To explain the distribution of the material according to geographical principles a few facts concerning the organization of the Maternity Service in Denmark will be given.

The number of public hospitals and hospital departments which admitted parturient women in the course of the ten-year period is 96. Of these 86 are surgical or mixed medical-surgical, while 10 are special maternity clinics with an obstetrician in charge.

These special maternity clinics in Denmark are distributed geographically with 7 in Copenhagen, one in Fyen and 2 in Jutland. They are concentrated within 5 of Denmark's 23 medical districts while the remaining 18 districts do not have any such special departments.

Of the deliveries, 40 per cent took place in the 5 districts where special clinics are available, 14 per cent within the special clinics themselves and the remaining 86 per cent in other hospitals, private clinics or in the patients' homes.

THE INCIDENCE OF CAESAREAN SECTION

The total number of births in Denmark in the ten-year period 1941—1950 was 858,842, the annual number steadily increasing until 1946, after which a slight fall is noticeable. The birth rate in Denmark is approximately 18 per thousand population.

The total number of abdominal Caesarean sections comprising full term or nearly full term infants (i. e. excluding abortions) during the ten-year period was 2,488, distributed according to a steadily ascending curve. The frequency of C. s. was 0.18 per cent in 1941 and 0.45 per cent in 1950.

The average figures for the frequency of C. s. in Denmark during the two five-year periods were 0.20 and 0.37 per cent respectively, i. e. the figures are nearly doubled during these years.

The details of the distribution of these operations within the 23 medical districts in Denmark must be excluded in this report due to limited space, but it should be mentioned that although the incidence of C. s. varied greatly within the separate districts — viz. between 0.06 and 0.48 per cent in 1941—45 and between 0.16 and and 0.61 per cent in 1946—50 — the average figures for the incidence of C. s. in the five districts where special maternity clinics are available show the same values as in the eighteen districts, where general surgeons determined the indications for operation.

From the Danish National Health Service (Director General: *Johs. Frandsen*, M. D.).

Table I.
Percentage frequency and maternal mortality of Caesarean section in Denmark.

	Number of births		Number of caesarean sections		Caesarean section frequency per cent		Number of postoperative deaths		Caesarean section mortality per cent	
	1941-45	1946-50	1941-45	1946-50	1941-45	1946-50	1941-45	1946-50	1941-45	1946-50
Whole country										
18 counties without maternity clinics...	253173	259929	512	958	0.20	0.37	45	35	8.8	3.7
5 — with — — ...	169905	175835	341	677	0.20	0.39	21	14	6.2	2.1
All 23 — without/with — — ..	423078	435764	853	1635	0.20	0.37	66	49	7.8	3.0
Maternity clinics										
Rigshospital A, Copenhagen	9366	9311	88	241	0.94	2.59	8	5	9.1	2.1
Rigshospital B, —	9782	10146	77	141	0.79	1.39	2	2	2.0	1.4
Comm. Clinic. Martinsvej, Copenhagen	10302	10658	0	0	0	0	—	—	—	—
Sct. Josef Hospital, Copenhagen	7539	10489	6	25	0.08	0.24	0	1	0	4.0
Diakonissestiftelsen, —	4228	3046	8	2	0.19	0.06	0	0	0	0
Frederiksberg Hospital, Copenhagen.....	0	2259	—	18	—	0.80	—	1	—	5 6
Sct. Lukas Hospital, Copenhagen	1083	1225	12	12	1.11	0.98	0	0	0	0
Maternity Clinic, Odense	2320	3026	46	67	1.98	2.21	2	0	4.3	0
— — Aarhus	10692	9058	37	43	0.35	0.47	3	1	8.1	2.3
— — Sønderborg	3374	3489	30	52	0.89	1.49	2	2	6.6	3.8
All maternity clinics in Denmark.....	58686	63007	304	601	0.52	0.95	17	12	5.6	2 0

This is illustrated in Table I, which also gives a more detailed picture of the position of C. s. within the ten Danish special maternity departments.

The incidence of C. s. varied greatly within these clinics viz. between 0 and 2 per cent in 1941—1945 and between 0 and 2.6 per cent in 1946—1950. The average figures for the incidence of C. s. for all special maternity clinics in the two five-year periods were 0.52 and 0.92 per cent respectively, figures which must be evaluated in the light of the fact that the three maternity clinics in Denmark with the greatest number of admissions, representing approximately half of the total number of deliveries within the special clinics, record as low an incidence of C. s. as 0.4, 0.2 and 0 per cent for the entire ten-year period.

In order to evaluate this type of analysis the principles applied abroad concerning this subject must be taken into consideration.

In Table II our Danish figures are tabulated against corresponding figures from foreign papers, a comparison, which, by the way is rendered difficult, because only two of the foreign reports, viz. T u r u n e n's (12) account from Finland (1938) and B e l a n o s c h k i n and M a l m n ä s's (1) more recent analysis of all Swedish Caesareans during the period 1946—50 base their C.s. frequency accounts in the same way as it is done in this paper, viz. on the *total* birth rate of the country concerned, while all the other statistics available from abroad record the C. s. frequency on a basis of the number of births *within* hospital departments and particularly within special maternity departments.

To obtain as satisfactory a basis for comparison as possible, Table II is, therefore, arranged in two sections, concerning whole country materials and maternity clinic materials respectively. In both sections, the materials are arranged in series according to increasing frequency of C. s. As might be anticipated, the percentage frequency of C. s. is lower in the materials for the whole country.

But simultaneously, the Table shows, that both the general incidence of C. s. in the whole country, and the average C. s. frequency in special maternity clinics is lower in Denmark than anywhere abroad.

When we in Denmark register 250 spontaneous deliveries for each C. s., while in adjacent countries only 110 spontaneous deliveries occur per C. s., and when the frequency of C. s. in our special maternity departments is one per cent, while elsewhere in the world such clinics operate with a frequency of between 2 and 6 per cent, or more, it will be understood that we Danes, seen through foreign eyes, are considered rather conservative in our midwifery.

Whether or not this be justified must be discussed later, when the prognosis of our cases is evaluated on a basis of an analysis of the indications for operation and the maternal mortality.

INDICATIONS FOR CAESAREAN SECTION

Table III illustrates how the present C. s. material is distributed according to the various indications for operation. It will be noted, that hemorrhage, contracted pelvis and toxaemia in both five-year periods have comprised the largest groups of indications. Placenta praevia and a few

Table II.

Survey of operative frequency, indications and maternal mortality in Danish and foreign Caesarean section materials.

	Period of time	Number of Caesarean sections	Caesarean section frequency per cent	Percentage distribution of various indications for c. s.			Caesarean section mortality of whole material per cent	Caesarean section mortality of various indications for c. s. per cent		
				placenta praevia	contracted pelvis	toxaemia		placenta praevia	contracted pelvis	toxaemia
Whole country materials										
Schou										
Denmark	1946—50	1635	0.4	28.7	19.6	7.1	3.0	2.3	1.9	10.3
Belanoschkin and Malmnäs										
Sweden	1946—50	5486	0.9	22.0	26.0	13.0	2.6	2.5	0.6	8.3
Turunen										
Finland	1938	943	1.2	11.7	46.4	16.7	3.7	—	—	—
Maternity clinic materials										
Schou										
All maternity clinics, Denmark	1946—50	601	1.0	25.5	21,6	5.2	2.0	2.0	1.5	6.5
Bosset and Frid										
Stockholm, Sweden	1949—52	146	1.8	11	35	2	0.7	—	—	—
Westman and Robbe										
Stockholm, Sweden	1943—51	462	2.3	12.1	37.2	5.2	1.7	—	—	—
Quigley										
Rochester, Monroe County, U.S.A.	1937—46	1693	2.4	8.7	24	6.1	0.9	0.7	0 8	2.9
Purdie										
Middlesex County, England	1943—47	1667	3.2	16.4	36.1	7.5	1.4	0 4	1.3	4.8
Naujoks										
Germany	1938	7024	3.3	16.7	47.2	12.1	5.3	—	—	—
Skajaa										
Oslo, Norway	1939—52	672	3.5	10.5	13.5	19.2	0.9	—	—	—
Vara										
Helsingfors, Finland	1946—50	1996	5.8	5.1	34.1	12.3	1.1	2.4	0.8	5.1
Marshall and Cox										
19 teaching hospitals, England	1943—47	7762	6.2	9.6	31	7.7	1.0	1.1	1.0	2.0

cases of accidental ante-partum hemorrhage have constituted the indications for approximately one third of the operations, 35 and 33 per cent respectively, in the two five-year periods. Contracted pelvis, together with the rather vaguely defined group cephalo-pelvic disproportion, obstruction due to abnormalities in the soft tissues in the pelvis and finally some few cases of threatened or manifest rupture of the uterus, constitute together a quarter of the indications for operation. Toxaemia was the indication for operation in 7 per cent of the material and various medical and surgical diseases in the mother in 4 per cent.

The last third of the material of C. s. comprises various complications which indicated C. s. to a great extent in the interest of the foetus. The Table shows that each of them is represented by a small per cent.

It will further be observed, that the percentage distribution recorded here has been fairly uniform in the two five-year periods. The few exceptions concern protracted labour, dystocia and foetal asphyxia. The general increase in the incidence of operation in the course of the ten-year period seems thus to have been particularly pronounced in operations performed predominantly in the interest of the foetus.

With regard to the three largest groups of indications, information is available concerning the total number of cases with these complications, and it is hereby possible to calculate the extent to which these cases were treated operatively, i. e. the percentage frequency C. s.

The figures appear from Table III. The increase of the C. s. frequency for placenta praevia from 29 to 40 per cent from the first to the second five-year period is significant even if it is not, however, of the same magnitude as the general increase, previously mentioned, in the incidence of C. s. during this period.

The C. s. frequency figures for contracted pelvis, viz. 8 and 14 per cent respectively may be considered somewhat more haphazard because of a rather varying interpretation of this conception in the different parts of the country, but if fairly uniform principles of diagnosis are presumed during the two five-year periods, it appears that the C. s. frequency for this group of birth complications parallels with the general increase in the incidence of C. s.

A similar lack of uniformity regarding definition and diagnosis prevails concerning toxaemia but even with such a reservation it is obvious

Table III. *Caesarean section frequency a*

	Percentage distribution of indications for caesarean section		Number of diagnosed cases	
	1941–45	1946–50	1941–45	1946–50
Placenta praevia	33.2	28.7	990	1186
Accidental ante partum haemorrhage	2 2	4.2		
Contracted pelvis	22.0	19.6	2421	2350
Cephalo-pelvic disproportion	2.2	3.1		
Rigidity of soft parts, tumours, etc. Ruptured uterus or threatened rupture	5.1	3.9		
Eclampsia, threatened or manifest	6.8	7.1	665	552
Various medico-surgical cases	4.4	3.4		
Malpresentation	4.0	8.0		
Elderly primipara	2.4	3.4		
Previous difficult labour, previous foetus death	3.1	4.0		
Previous caesarean section	0.2	1.1		
Prolonged labour, uterine inertia with or without foetal asphyxia	1.8	6.1		
»Difficult labour«. Miscellaneous	3.3	6.3		
No diagnosis	9.3	1.1		
	100 %	100 %		

that with regard to this complication a pronounced increase in the frequency of operation has occurred, viz. from 9 to 21 per cent.

The figures in brackets in the Table give an impression of the C. s. frequency in the various districts in Denmark. The figures *above* the average figures, just mentioned, for the entire country indicate the incidence of operation in the 18 districts without special maternity clinics while the figures *under* the average values concern the incidence of C. s. in the 5 districts with special maternity clinics.

Concerning placenta praevia, the principles of treatment throughout Denmark were fairly similar, although the tendency to operative treatment seems to be slightly less in those districts where the obstetricians' indications play a part, than in the remaining purely surgical districts.

This more conservative attitude on the part of the obstetricians has obviously influenced the treatment of contracted pelvis and may be traced concerning the cases of toxaemia in recent years also.

As very few foreign papers emphazise figures similar to these just recorded concerning the percentage C. s. frequency in the various birth complications we must use the *percentage* distribution of indications for operation as the basis for a comparison of Danish and foreign principles for indications.

In Table II, the Danish figures, previously mentioned, are tabulated against corresponding figures from foreign materials, and it appears from this that the Danish distribution of the incidence of C. s. (and this holds true for the total material from the entire country as well as for the material from special maternity clinics) is characterized by a relatively frequent occurrence of complicating hemorrhage, while contracted pelvis and toxaemia are represented less in the Danish than in foreign materials.

The present investigation thus reveals that there is a considerable difference between the Danish and the foreign principles for indications for operation. Consequently, the question arises whether we in Denmark are right, a question which, however, can hardly be answered before the second and most decisive factor in the prognosis of C. s., viz. the mortality of the patients, is analyzed.

THE OPERATIVE MORTALITY

As the information available concerning the infantile mortality in connection with C. s. in Denmark has been inadequate for statistical analysis, it has been possible to treat only the maternal mortality.

In Table I is recorded the number of mothers who died following C. s. in Denmark in the two five-year periods together with the percentage mortality for C. s. Out of the 2.488 mothers who underwent C. s., 115 died, viz. 66 in the first and 49 in the second five-year period, indicating a maternal mortality for the entire material of 4.6 per cent, i. e. 7.8 per cent in the first and 3.0 per cent in the second five-year period.

This fall in the mortality for C. s. throughout the ten-year period must obviously be evaluated in connection with the *general* decline in maternal mortality associated with delivery in the course of this period.

ortality of the various complications of delivery.

Number of caesarean sections		Caesarean section frequency per cent		Number of postoperative deaths		Caesarean section mortality per cent	
1941—45	1946—50	1941—45	1946—50	1941—45	1946—50	1941—45	1946—50
						%	%
285	471	$28.8 < \frac{(30.3)}{(26.4)}$	$39.5 < \frac{(42.6)}{(37.0)}$	25	11	8.8	2.3
12	41			3	1	25.0	2.4
189	322	$7.8 < \frac{(10.9)}{(5.3)}$	$13.7 < \frac{(18.6)}{(10.4)}$	8	6	4.2	1.9
19	53			0	1	0	1.9
44	65			1	1	2.3	1.5
59	117	$8.9 < \frac{(8.1)}{(10.0)}$	$21.2 < \frac{(23.6)}{(18.0)}$	12	13	20.3	10.3
38	59			6	2	13.5	3.4
34	133			3	2	8.8	0.8
21	57			3	2	14 3	3.5
26	72			1	2	3.9	4.1
2	20			0	0	0	0
16	101			3	4	18.8	4.0
28	104			1	3	3.6	2.9
80	20			0	1	1.2	5.0
853	1635						

In a previous study (3), it was recorded that the general maternal mortality on delivery in Denmark fell from 1.7 per thousand in 1941 to 0.6 per thousand in 1950. The mortality on delivery per vias naturales showed a similar fall from 1.5 to 0.5 per thousand and, finally, an account year by year concerning the percentage maternal mortality following C. s. (expressed as number of deaths per number of operations) showed that the reduction in this mortality in the course of the ten-year period occurred according to a steadily descending curve from 9.4 per cent in 1941 to 1.9 per cent in 1950. In other words, while in Denmark the general maternal mortality in the course of the ten-year period was reduced by approximately 66 per cent, the mortality for C. s. was reduced simultaneously by approximately 80 per cent.

But, on the other hand, the calculations show that the maternal mortality following C. s. comprises a steadily increasing part of the total maternal mortality in this country, viz. from 10 per cent in 1941 to 15 per cent in 1950, a circumstance which probably is related to the greatly increasing incidence of the operation.

If Danish conditions in this field are compared with corresponding foreign conditions, it appears from Table II that the maternal mortality following C. s. has been greater in Denmark after 1945 than in foreign countries as indicated in the available foreign materials, and this holds true both for our material from the entire country and for the material from special maternity clinics.

It must, however, be noted that in Table II only a relatively small number of the more recent foreign papers are recorded. V a r a (10) records an extensive review concerning 24 papers on C. s. from various countries back to 1930 and from this it appears that a roughly calculated average value for the mortality following C. s. abroad in these years is about 1.5 per cent.

Although in the majority of these foreign communications, as previously mentioned, the results are based upon materials from special maternity clinics, the Danish maternal mortality following C. s. with average values for the five-year periods 1941—1945 and 1946—1950 of 7.8 and 3.0 per cent respectively, must be regarded as seriously high, a fact which becomes the more striking when compared with the fact that the Danish general maternal mortality following delivery is very low.

In the present study details have been omitted regarding the question of the *distribution* of the operative mortality within Denmark, but the last column in Table I gives an impression of the conditions regarding this point. It will be observed, that the maternal mortality was less among the patients, operated upon in the districts where special maternity clinics were available, than among the cases which were treated in the other districts of the country.

As, however, it can scarcely be quite correct to pronounce identical judgement on the prognosis for the two categories of materials of hospitalized patients, so different in their composition, the death rate among the mothers who were operated upon in the two geographically different groups of the population has been calculated on a basis of the total number of births in the parts of the country concerned. The result arrived at (not recorded in the Table) was that while in

1941—1945 18 women died following C. s. for every 100,000 births in districts *without* special maternity clinics, the corresponding figure in districts *with* special maternity clinics was 12. A corresponding calculation for the second five-year period 1946—1950 shows that in districts without special maternity clinics 13 deaths occurred following C. s. among 100,000 mothers, while the number of deaths for the same number of births in districts with special maternity clinics was 8.

Thus 50 per cent more mothers died following C. s. in the 18 districts of the country (representing more than half of the women of the country) which do *not* have access to special maternity clinics than in the 5 districts where the special maternity clinics are concentrated.

The maternal mortality of C. s. in this country *among the various complications of delivery necessitating operation* appears from Table III, and in Table II are the same figures for the three most important indications, placenta praevia, contracted pelvis and toxaemia, tabulated for the period 1946—50 and compared with the corresponding statistics from abroad.

Table III shows that the decrease in the mortality for C. s. mentioned above, is reflected in all groups of indications, although to a varying extent.

The operative mortality in the cases of *placenta praevia* is reduced from 8.8 to 2.3 per cent so that it is now of the same order as that in the Swedish national material, just as the mortality for operation in cases of placenta praevia in our special maternity clinics corresponds to that recorded by V a r a (10) from a special maternity clinic in Finland.

It may further be stated, that calculations have shown that the operative mortality among cases of placenta praevia in Denmark has constituted a diminishing fraction of the total mortality for placenta praevia in the course of the ten-year-period. The figures were 47.2 per cent in 1941—45 and 19.6 per cent in 1946—50 respectively (not recorded in the Tables).

With regard to *contracted pelvis*, the C. s. mortality was 4.2 per cent and 1.9 per cent respectively in the two five-year periods, and it appears from Table II that these figures from the entire country as well as those from our special maternity clinics are expressions of a Danish maternal mortality in this complication of delivery, distinctly higher than abroad.

As regard the third of the large groups of indications, *toxaemia*, Table III conveys a serious reminder of the large operative mortality for this complication of pregnancy.

As the terminology within the group of cases of toxaemia has varied somewhat in the different hospitals throughout the country, it has been impossible to obtain definite information concerning the number of patients who had real convulsive attacks for which reason it can be recorded only with reservations that the percentage operative mortality for manifest eclampsia in Denmark has been as high as 24 and 11 per cent respectively in the two five-year periods. The calculation of the percentage of the maternal mortality for *all* cases of toxaemia operated upon is more reliable. These figures, which are the ones recorded in Table III, are also very high, viz. 20.3 and 10.3 per cent respectively, and it appears from Table II that the maternal mortality for cases of toxaemia is higher in Denmark than abroad. And this is the case both in our whole-country material and among the patients within our maternity clinics.

In addition it may be stated, on the basis of material available from the National Health Service, that the *general* mortality among eclamptic mothers in the two five-year periods was as high as 21.2 and 16.8 per cent respectively.

If the contribution paid by the operative mortality to the total mortality due to eclampsia be calculated, the figures 8.5 per cent and 14 per cent for the two five-years periods are arrived at (not recorded in the Tables) which is an expression of the fact that the mortality due to C. s. plays an increasing part in the total mortality due to eclampsia.

As regards the other groups of indications, the reader is referred to Table III. Here it is only pointed out that although a distinct improvement is noticeable in the maternal prognosis for the operations carried out predominantly in the interest of the infant (probably associated with the great increase in the incidence of the operation in this field, previously mentioned), operative delivery of difficult, prolonged labour still involves a maternal mortality of 3—4 per cent.

As part of the investigation on the mutual relationship between the causal condition, i. e. the complication of d e l i v e r y concerned, and the actual complications of the o p e r a t i o n s as regards their influence upon the maternal mortality, an account was given in a previous study (3) of the immediate causes of death in the 115 cases which ended fatally. It appeared, that paralytic ileus was responsible for 24 per cent of the post-operative deaths, slightly less in the first five-year period and slightly more in the second. Peritonitis, sepsis, embolism and an isolated case of phlebitis, i. e. direct or indirect conditions of inflammation, were the cause of 26 and 41 per cent respectively of the operative deaths; of these, embolism were responsible for 12 and 22 per cent respectively. Death due to hemorrhage, atony, and shock comprise a total of 14 per cent of the mortality figures and, as might be anticipated, more in the first five-year period than in the second, viz. 19 and 10 per cent respectively. Eclampsia appears to have been directly responsible for approximately 11 per

Table IV.
Distribution of the causes of death.

Indications for operation	Number of postoperative deaths	Causes of death Complications of delivery Postoperative complications		
Placenta prævia	36	Uterine inertia, Hemorrhage, Shock	12	
		Ileus		5
		Infection		9
		Embolism		7
		No diagnosis		3
Contracted pelvis	14	Ileus		8
		Infection		3
		Embolism		1
		Cardiac insuff.		2
Toxaemia-eclampsia	25	Eclamptic state	13	
		Ileus		4
		Infection		3
		Embolism		3
		Shock		1
		Cardiac insuff.		1
	75	Death from complications of delivery	25	
		Death from postop. compl.		50

cent of the maternal deaths, viz. 14 per cent in the first five-year period and 8 per cent in the second. Finally, the last 12 per cent of all causes of deaths were divided partly among isolated cases of which 4 deaths were due to cardiac insufficiency and partly among cases of which no information was available.

On a basis of this distribution of the causes of death, it was considered justifiable to conclude that the original condition i. e. the birth complication was responsible for death in a minority of the cases, mainly the cases of hemorrhage and toxaemia, while the actual complications of operation are responsible for the greater part, nearly two thirds, of the postoperative deaths, mainly paralytic ileus, peritonitis, sepsis and cases of embolism.

Finally, in accordance with the principle followed in this report of concentrating the analysis mainly on the three largest groups of indications, viz. placenta praevia, contracted pelvis and toxaemia, the causes of death of the 75 patients who died following operation in these groups will be recorded in tabular form.

As might be anticipated, the picture differs for the three complications concerned. With a distribution in accordance with the principles recorded above, the original condition must be considered responsible for one third of the fatal cases of placenta praevia, for none of the fatal cases of contracted pelvis, for approximately half of the fatal cases of toxaemia and, in accordance with that which was stated above concerning the entire material, for approximately one third of the total 75 fatal cases.

SUMMARY, CONCLUSIONS AND DISCUSSION

With the object of drawing conclusions from this communication regarding the future position of C.s. in Danish obstetrics, the main points in the observations recorded above will be reviewed and discussed briefly. The following facts may be pointed out:

2,488 cases of C.s. were carried out in the course of the ten-year period 1941—1950 in 96 Danish hospital departments, distributed over the entire country. 906 of the operations took place in Denmark's 10 special maternity clinics.

The incidence of C.s. in Denmark, viz. 0.20 per cent in 1941—1945 and 0.37 per cent in 1946—1950, is increasing, but both the general incidence of C.s. and the incidence of operation in our special maternity clinics (now 0.95 per cent) are considerably lower than what is usual abroad.

Placenta praevia, contracted pelvis and toxaemia were, in the order mentioned, the most common indications for operation. Placenta praevia constitutes a relatively greater part of the indications for operation in Denmark than in the majority of foreign materials. Contracted pelvis constitutes a relatively smaller part, and this holds true also of toxaemia. The differences between Danish and foreign principles regarding the indications for operation are, on the whole, considerable.

As regards the absolute incidence of operation, it may be calculated that during the second five-year period, placenta praevia was treated operatively in 40 per cent of the cases, contracted pelvis in 14 per cent and toxaemia in 21 per cent of the total number of cases diagnosed.

The incidence of operation for these three groups of indications was less in the districts with special maternity clinics than elsewhere in Denmark.

The general mortality for C.s. in Denmark, viz. 7.8 per cent in 1941—1945 and 3 per cent in

1946—1950 is diminishing but is still higher than is usual abroad.

The maternal mortality in Denmark for cases of placenta praevia, viz. 3.3 per cent, now seems to be in accordance with the figures stated abroad, but our operative mortality both for contracted pelvis (1.9 per cent) and for toxaemia (11 per cent) is larger than are the corresponding figures from abroad.

The mortality for C.s. in Denmark is higher in those districts of the country in which no special maternity clinics are available (3.7 per cent) than in the districts with such clinics (2.1 per cent).

Roughly speaking, the original pathological condition of the mothers was responsible for a minority of the post-operative deaths while the actual complications of operation were responsible for the fatal issue in nearly two thirds of the fatal cases in the material.

The most striking feature in our Danish material, as compared with foreign accounts, is the high maternal mortality in Denmark. The fact that it is decreasing considerably is probably mainly connected with the numerous factors which in recent years have favoured the development of surgery in general, modern principles of pre- and post-operative treatment, improved equipment for transfusion, anaesthesia and chemotherapy.

There can be no doubt that the significant increase in the incidence of C.s. in the course of the ten-year period has also influenced the operative mortality favourably and the same holds true for the improvement in the operative technique itself, i. e. the transition from the classical to the lower segment C.s., a technique which in the present material has been adopted principally within the special maternity clinics but which should undoubtedly gradually be introduced throughout the entire country.

In connection with the question of the significance of the incidence and technique of operation for the maternal prognosis, attention must be drawn to an essential point in connection with the organization of the Maternity Service in Denmark.

It has repeatedly been mentioned, that the Caesarean section frequency is low in Denmark. If we take in consideration, that our Danish C.s. cases, less than 2500 in number, have been distributed over approximately 100 departments in the course of ten years it will be understood, that each surgeon only has had the opportunity of performing this special operation a couple of times annually. This fact, together with the condition pointed out above, that the mortality from C.s. was less among the mothers in the few districts of the country where special maternity clinics are available than in the remainder of the country, justifies the assumption that the prognosis for C.s. in Denmark can be improved if the treatment of obstetric complications becomes more centralized and specialized than is the case today.

As regards indications, good results have been achieved in Denmark in placenta praevia with a relatively high incidence of operation. By analysis of our material, which comprises all the cases of placenta praevia, both total and partial, it has been verified that the prognosis is better for the cases operated upon than for the cases treated conservatively. Considering the fact that in Denmark one third of the maternal mortality in connection with delivery per vias naturales are due to complicating hemorrhage, there should scarcely be any hesitation in extending the indications for operation to include also *partial* placenta praevia beyond what is the case today.

The fact that contracted pelvis is represented by a relatively small number of cases in our Danish operative material may be due to the circumstance that the incidence of rickets is less in Denmark than in many places abroad. The fact that our cases are associated with such a relatively high mortality may be ascribable to the circumstance that we have both established the diagnosis, and operated, too late. The increasing antenatal care in Denmark ought to create favourable conditions for improvement on this point.

In the Danish material, the cases of toxaemia are also associated with a low incidence of operation and a high mortality, measured by international standards.

As this condition *per se* has such an excessively high mortality, irrespective of whether the treatment be conservative or operative, and as the original condition itself is often the cause of death in cases in which death ensues following operation, it is understandable that the future trend must be toward greater conservatism in the treatment of cases of toxaemia and particularly where manifest eclampsia is present.

Finally, considering under one heading the mixed group of complications of delivery which have caused C.s. primarily in the interest of the child, it appears that these operations, despite improvement in recent years, still show a maternal mortality of approximately 3—4 per cent which is a warning to exercise restraint corcerning C. s. in the interest of the infant if a prolonged pre-operative labour, or other conditions, involve an increased operative risk for the mother.

In conclusion it may be pointed out that although an analysis such as this could not be complete on all points its presentation was considered justified, principally because it clearly speaks in evidence of the fact that C.s. is a method of treatment which p e r s e involves a maternal mortality, which to date has been too high in Denmark.

The possibilities for improving the prognosis of C. s. in Denmark must be sought by altering the principles of operative delivery in the direc-

tion of more operations in complicating hemorrhage, fewer operations in toxaemia, earlier operation in contracted pelvis and greater centralization of the operations in general.

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BRONCHIAL CARCINOMA — A PANDEMIC

By JOHANNES CLEMMESEN

Isaac Adler from New York, who, obviously with some difficulty, in 1912 collected 374 cases of lung cancer for a well known monograph (1) states that he shares the belief with many others that there is no absolute increase in the incidence of carcinoma, but he finds that the incidence of malignant neoplasm of the lung seems to show a decided increase although still out of all proportion to the frequency of other malignant neoplasms, as for example of the female breast or the stomach. Nowadays, figures from various countries show bronchial carcinoma among the outstanding neoplastic diseases. Thus, since 1947 this carcinoma ranks as the most frequent among the male sex in Copenhagen.

Adler further states that »it has always been maintained that males are by far more frequently subject to lung tumours than females«, and his own cases, when »sarcomata« are included, show a sex ratio of 3: 1. He mentions that the domestic life led by women and the more unprotected life of men, the abuse of tobacco and alcohol, the many trades and vocations which are accompanied by irritation of the respiratory organs etc. have been accused in explanation of the excess of lung tumours among males, but he finds that the entire subject is not ready for final judgement.

REALITY OF INCREASE IN CASES

The greater part of the increase in frequency of cancer of the lung, reported from the first years of this century, may well have been apparent only and caused by the prolongation of the average length of life together with progress in diagnostic technique, but it should be realized that we cannot expect the latter to change the sex ratio for cancer of the lung.

Statistical studies on this subject have usually shown an increase, but they have mostly been based on materials from one or more hospitals, which can not give any final information about the incidence of disease, unless the hospitals serve well delimited populations, treating all their cases, so that it is possible to measure and describe the population from which the cases have arisen, particularly with regard to age distribution. Also authors making use of autopsy records have most often disregarded the danger of selection in such materials both on admission, and on treatment, and performance of autopsy. Even information on sex ratio, which often is unstated, may be insufficient if the number of hospital beds is not the same for the two sexes.

In Denmark autopsy records from Rigshospitalet were thoroughly studied in 1936 (14, 15) and 1942 (11). It appears that the percentage of bronchial carcinoma in this material cannot have begun to rise earlier than 1926, and that the rise is doubtful up to 1930. A small study from Aarhus in 1935 (32) showed similar features, but possibly due to chance, since female cases numbered twice the male.

The Danish Cancer Registry in 1947 (3) compared the rate of cases of bronchial cancer found among patients examined in the Central Tuberculosis Dispensary in Copenhagen, and the rate of deaths from cancer of the lung reported from this city 1931—1945. It was concluded that even a pronounced increase in crude mortality rates for cancer of the lung among males does not necessarily mean a real increase in incidence. This conclusion was drawn, because the number of cases diagnosed in the Tuberculosis

From the Danish Cancer Registry under The National Anti-Cancer League.

Dispensary did not show a rise corresponding in magnitude to the increase in death rates, which after 1941 became particularly rapid affecting both sexes almost proportionately. Just at this time special services for thoracic surgery were opened and systematic bronchoscopy was introduced.

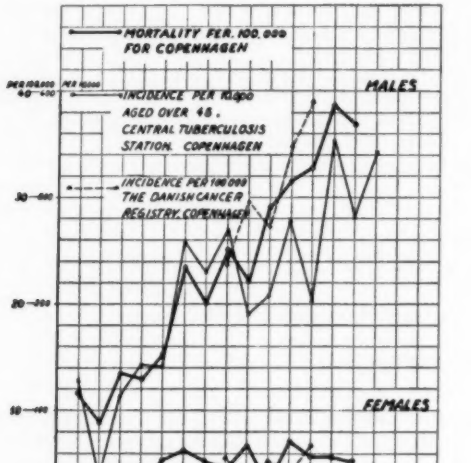


Fig. I.
Cancer of the Lung in Copenhagen.
Full line: Mortality per 100.000.
Thin line: Incidence per 10.000 aged over 45, Central Tuberculosis Dispensary, Copenhagen.
Dashed line: Incidence per 100.000, The Danish Cancer Registry.

Note: The rates given for cases of bronchial cancer found among the patients examined in the Tuberculosis Dispensary have been divided by 100 because of the higher values expected for persons aged over 45 and largely suffering from chest trouble at first examination. Figures have further been displaced one year in order to allow for the period between diagnosis and death.

However, the picture changed when the material was extended to comprise the following five years, and when roentgenograms from the Tuberculosis Dispensary had been revised in the light of the later fate of patients, including bacteriological results from the State Serum Institute and autopsy results from hospitals. It now appeared that the sudden increase in crude death rates after 1941 was followed by a continuous increase in rates for men, so that the former simply amounted to a steepening of the slope, which now was reflected exactly similarly in both materials. The curve for women, after a temporary rise in the same period resumed its roughly horizontal trend, as seen in fig. VI.

It appears from fig. I that the morbidity rates found by the Cancer Registry for the period of 1943 to 1947 showed an increase parallel to the increase in death rates, while during these years there were no changes in the percentage of hospital admissions for lung cancer, nor of histological or autopsy examinations of patients admitted, as shown in table I. Therefore, if better diagnosis were the explanation of the increase in cases diagnosed, it should be due to increased medical attention, applied proportionately to these various procedures, which may be excluded since the same increase appeared for cases of bronchial cancer in the material of the Tuberculosis Dispensary, which had been revised retrospectively under constant conditions, and originated from patients referred from practising physicians primarily with a view to a different disease.

Table I.
The Danish Cancer Registry 1943—47.
Carcinomas af Bronchus and Lung (162.1 and 163).
Verification of diagnosis.
Capital.

Men.

Year	All cases	Admitted to hospital per cent.	Histologically verified per cent. of		Autopsies per cent. of	
			all cases	hosp. cases	all cases	deaths
1943	96	94	64	68	65	66
1944	129	95	60	64	62	62
1945	120	93	60	65	60	61
1946	150	91	59	65	59	63
1947	172	92	65	70	57	60
Total	667	93	62	67	60	62

Already from a clinical point of view it would appear improbable from a glance at the graphs that diagnostic improvements should cause a steady rise in the number of cases diagnosed, limited to the male sex and continuing through a period of twenty years, at an annual rate of about 12 per cent in Copenhagen. On the other hand, the particular increase after 1941, which affects both sexes, must probably be due to rounding-up of more cases.

It was therefore concluded on the basis of these studies that the increased incidence of bronchial carcinoma in Denmark during the last decades must be real, at least so far as it is confined to the male sex.

Note: It should be mentioned that documentation of all Danish figures used for this paper will be found in a paper by Clemmesen, Nielsen and Jensen (5), and that conclusions have been based on statistical computations by Arne Nielsen, lic. act., testing deviations for each age group separately. Detailed comparisons have been made of figures for death certificates and notifications to the Cancer Registry, in order to ensure the justification of using the death certificates for the further studies summarized in the following. Thus, the graphs given in this text serve as illustrations only, and particularly in so far as they represent crude mortality rates.

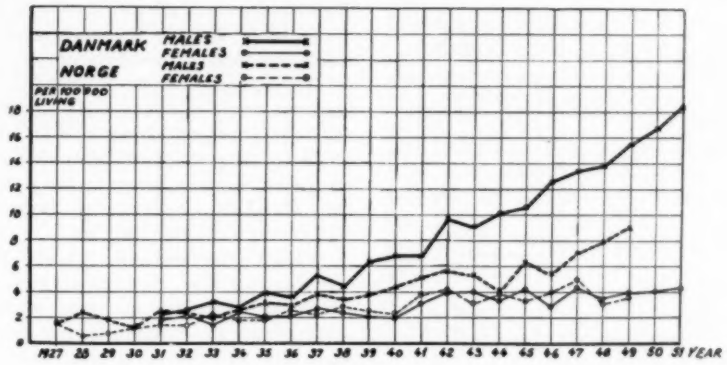


Fig. II.
Cancer of the lung in Norway and Denmark, 1927 to 1951.
Crude mortality rates for men and women per 100.000 living.

INCREASE IN RATES FOR WOMEN?

International comparisons of crude mortality rates for cancer of the lung can only be made with some reservations. Differences in incidence between age groups, and between urban and rural areas, reduce the value of materials not subdivided with regard to these factors, and in some countries metastatic tumours have until recently been classified together with primary bronchial carcinoma.

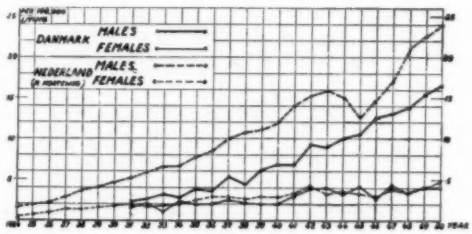


Fig. III.
Cancer of the lung in the Netherlands and Denmark, 1924 to 1950.
Crude mortality rates for men and women per 100.000 living.

In spite of these sources of error, we find, however, as illustrated in figs. II and III a close similarity between crude mortality rates for women in Norway (36), Holland (18), and Denmark (5). No doubt, this close similarity of unadjusted rates is conditioned by the facts that bronchial carcinoma in women does not increase in frequency with age as steeply as for men, nor does it show as great differences in incidence between urban and rural areas. But it should be remembered that just these features are most pronounced where the increase in cases among the male sex is most distinct. It therefore seems that, so far, the increase in mortality from cancer of the lung among women cannot be demonstrated in Holland, Norway and Denmark.

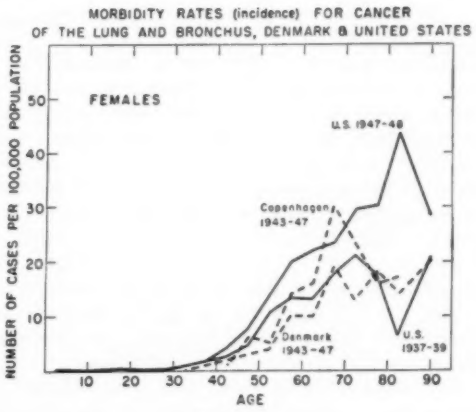


Fig. IV.
Dorn: Cancer of lung and bronchus in Denmark and U.S.A., 1937 to 1948.
Morbidity rates for women at various ages per 100.000.

A comparison of morbidity rates at various ages for bronchial cancer among women in Denmark and the United States, by D o r n (10), nevertheless, shows higher rates for American women, than for Danish, which suggests a beginning increase among the former. It may therefore be realistic to regard the absence of a major increase among European women as temporary only.

INCIDENCE IN URBAN AND RURAL AREAS

A similar view may, anyhow as far as Denmark is concerned, be taken on the present difference, observed in most countries, between urban and rural areas with regard to the incidence of bronchial cancer.

Crude death rates for men in Greater Copenhagen have risen from 4.5 in 1931 to 36.9 in 1950 against corresponding values of 2.1 to 13.5 for provincial towns, and 1.6 to 10.1 in rural areas. As suggested by fig. V, and further supported by studies on age distribution described later, this

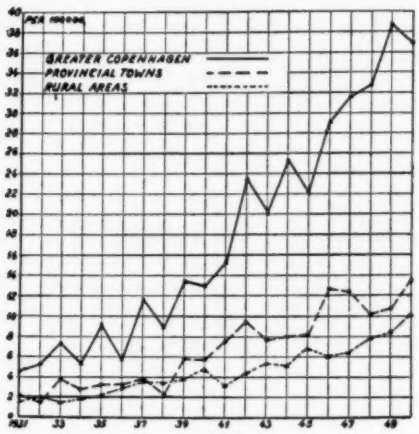


Fig. V.
Cancer of the lung in Denmark, 1931 to 1950. Crude mortality rates for men in capital, provincial towns and rural areas per 100.000 living.

difference may be explained as the result of a delay of the carcinogenic influence in provincial towns and rural areas. Death rates for women show slightly higher values for the capital than for rural areas, and whether apparent or real, this small difference seems constant, so that it might be explained as caused either by some atmospheric influence, or by slightly better medical facilities in the towns. But apart from this questionable observation nothing has been found in the Danish material in justification of the assumption of an effect of town air favouring the development of bronchial carcinoma.

In England, Stocks has demonstrated a parallelism between the degree of air pollution in towns and mortality from cancer of the lung (30, 31), and has tentatively suggested that carcinogens in the air might support the effect of stronger carcinogens of different origin. At the same time, Mills and Porter (25) found the consumption of cigarettes larger in the central quarters of Columbus, Ohio, with their more polluted atmosphere, than in the cleaner suburbs.

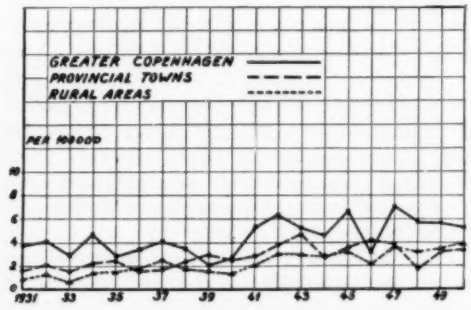


Fig. VI.
Cancer of the lung in Denmark, 1931 to 1950. Crude mortality rates for women in capital, provincial towns and rural areas per 100.000 living.

Recent demonstrations of carcinogens in filtrates from town air, by Kennaway and Waller (16), and others, certainly point to the importance of smoke abatement. . We would also expect carcinogens connected with the presence of soot. However, Danish figures concerning carcer of the lung from districts free of air pollution, such as the rural areas, leave no hope so far of avoiding any significant part of the increase in incidence by excluding these factors.

Within Copenhagen, which has very clean air for its size, bronchial cancer among men shows a distribution very much like cervical carcinoma in women, being more frequent in districts with lower house rent, whichever their location in the city, and for the years 1943 to 1947 particularly so among middle-aged men.

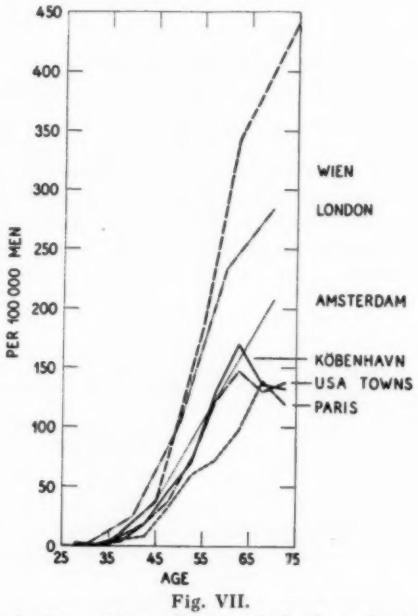


Fig. VII.
Louvain Symposium: Cancer of the lung in various cities ca. 1945—50. Mortality and incidence rates for men at various ages per 100.000.

AGE DISTRIBUTION OF INCREASE

An international comparison of incidence and mortality rates, — which for the period in question amount nearly to the same — may be made on the basis of material from various cities, collected for the International Symposium on the Endemiology of Cancer of the Lung, held in Louvain, July 1952 by the Council for International Organizations of Medical Sciences (21).

The graph, fig. VII, suggests the formation of a peak in curves running at lower levels, which tends to be smoothed out at higher levels. A closer analysis of mortality rates for Vienna (20), in fig. VIII confirms this impression, and an

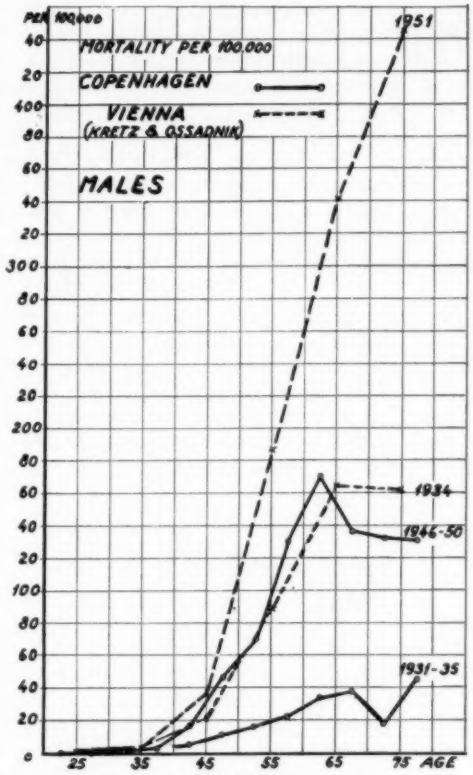


Fig. VIII.
Cancer of the lung in Vienna and Copenhagen, 1931—35 and 1946—51. Mortality rates for men at various ages per 100.000.

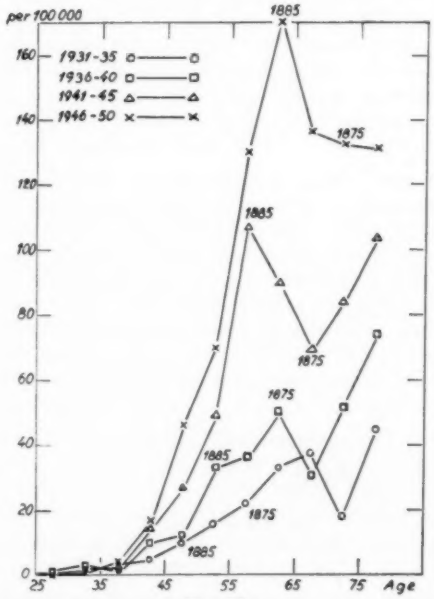


Fig. IX.
Cancer of the lung in Copenhagen, 1931 to 1950. Males. Mortality rates at various ages for quinquennial periods, per 100.000 living.

analysis of mortality rates at various ages for Copenhagen will give the explanation.

Fig. IX illustrates that the increase in mortality rates for cancer of the lung in Copenhagen, at present is heaviest among middle-aged men, but at the same time it appears, that as the heavily afflicted age groups grow older, the rise in rates will subsequently move to older age groups, so that finally the shape of the age distribution curve for all men in Copenhagen, as in Vienna, will approach the usual classical shape for extragenital cancers.

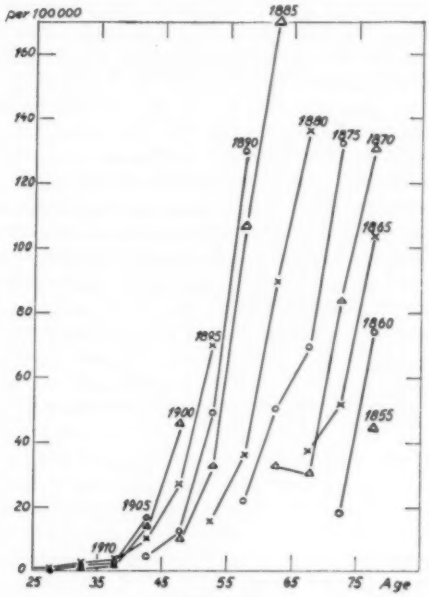


Fig. X.
Cancer of the lung in Copenhagen, 1931 to 1950. Males. Mortality rates at various ages for quinquennial groups born about the year indicated, per 100.000 living.

Fig. X represents the same observations as fig. IX, but the lines have been drawn so as to connect observations made on the same five-year groups, a method of subdivision first applied in statistics on cancer of the lung, by K o r t e w e g (17, 18). It appears that the age distribution curves for the birth groups as far as the examined period goes, keep the classical shape with considerable constancy, taking a parallel course. It also appears that the later groups have been born, the ealier in life the cancer will appear, so that the curve will run at a higher level, representing an increase in risk, which seems particularly pronounced for men born about 1885 as compared with those born about 1875. A corresponding diagram for provincial towns, fig. XI, shows corresponding by wide intervals between the curves, but here the narrowing seems a little postponed, apparently not taking place before birth groups 1890 or 1895, which, if finally confirmed, will be in harmony with the

delayed increase in mortality rates for provincial towns and rural areas, already discussed.

The reality of this delay, which makes it unnecessary to assume a »co-carcinogenic« effect of town air under Danish conditions, is further evidenced by an analysis of the character of the increase in age-specific rates, illustrated in figs. XII, A—B, which show schematically how the classical age distribution curve for extragenital cancer may develop according to more than one principle. Fig. XII »A« illustrates the overall effect of a carcinogenic agent applied anew and affecting all age groups equally, as for instance atmospheric pollution would be supposed to do. »B« illustrates the effect of a new agent affecting all groups born later than a certain point of time. The final age distribution may be the same as in fig. »A«, but the pattern of the development is principally similar to fig. IX, and here we are probably dealing with an additional increase in the intensity of the carcinogenic effect, being stronger the later the group has been born and causing a slight displacement of the curves to the left. Further modifications may be caused, if, for instance, a number of persons in older groups have been affected, too.

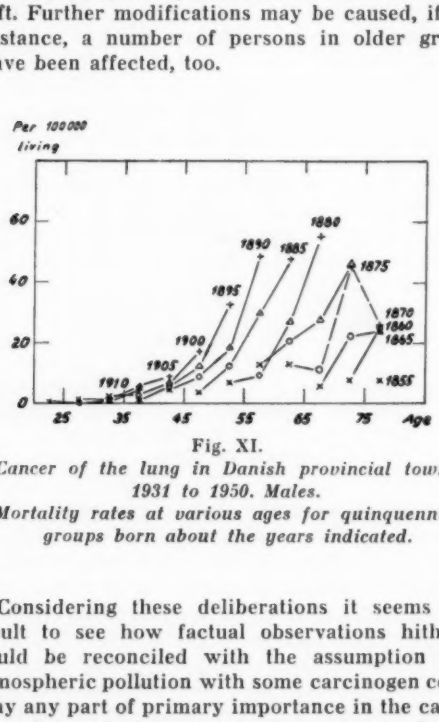
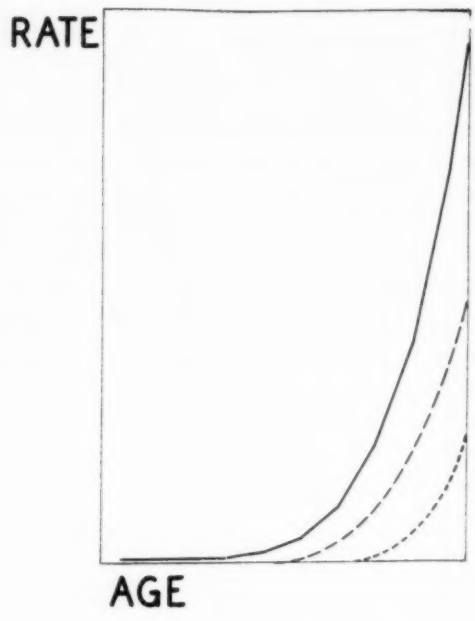


Fig. XI.
Cancer of the lung in Danish provincial towns, 1931 to 1950. Males.
Mortality rates at various ages for quinquennial groups born about the years indicated.

Considering these deliberations it seems difficult to see how factual observations hitherto could be reconciled with the assumption that atmospheric pollution with some carcinogen could play any part of primary importance in the causation of bronchial carcinoma among men in Copenhagen, quite apart from the problems involved in the apparent immunity of women to an agent of such universal nature. It seems hazardous to go any further than Stock's original concept of atmospheric pollution as a possible supporter of other carcinogenic effects, and as far as Denmark is concerned, it seems impossible, so far, to demonstrate any sign that even complete abatement of air pollution would reduce the increase in bronchial carcinoma among men.



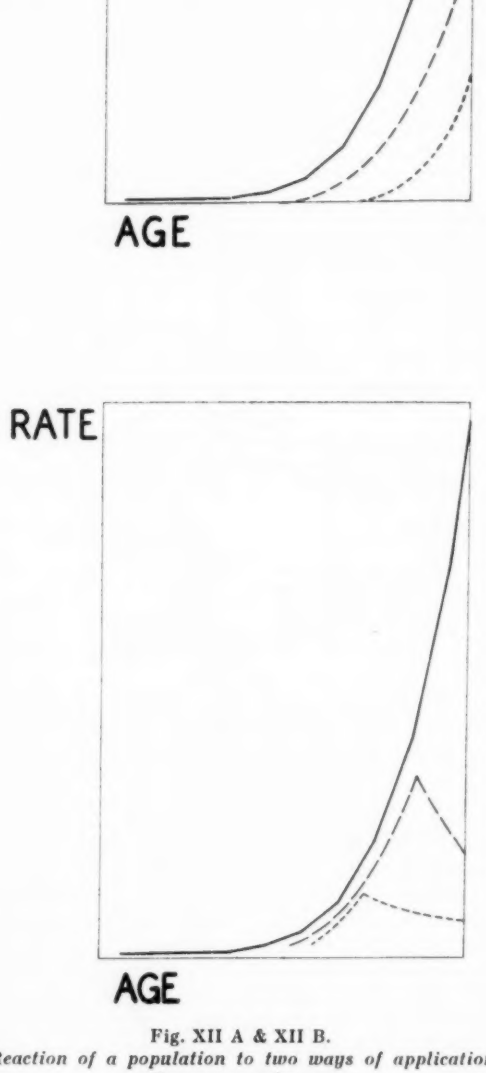


Fig. XII A & XII B.
Reaction of a population to two ways of application of a new carcinogen.

A. Exposure of all age groups to atmospheric pollution.
B. Exposure of birth groups from a fixed age to a carcinogen showing some increase in intensity as in birth groups tobacco smoking.

THE AVERAGE MINIMAL PERIOD OF EXPOSURE

Studies on cases of bronchial carcinoma caused by radioactive air among miners in Schneeberg and Jachymow have shown that under the local conditions a period of exposure of seven to twenty years is required for the development of the disease (12). Most often this period is not less than ten years. Other casuistics have shown a true »latent period« amounting to between ten and eighteen years, after which time a delayed cancer may develop, even if exposure to the carcinogen has been discontinued.

In man these well-defined values can only be estimated by individual observations, but the results represented in fig. X give us an opportunity for a tentative estimate of the average minimal period necessary between the beginning of exposure and the death of the patient from cancer of the lung, under conditions as in Copenhagen.

In 1931 mortality from cancer of the lung in Copenhagen amounted to 4.5 and 3.7 per 100,000 inhabitants for men and women respectively. In view of this small difference in rates between the sexes it may be assumed that the increase for men is unlikely to have started much earlier than 1930. As illustrated in fig. X even the birth groups with the highest mortality do not show an increase in rates until after the age of 35. Whether the carcinogenic influence is determined by customary, occupational or hormonal factors it seems reasonable to assume that usually it does not commence effectively before the age of 15 or perhaps a few years later, so that it will be justified tentatively to assume an average minimal period of about twenty years from the beginning of the exposure to the death of the patient from cancer of the lung, under conditions as in Copenhagen. Allowing for wider variations either way it may therefore be assumed that the carcinogenic influence discussed, did not begin later than 1910.

As already mentioned, the group born about 1885 must have been exposed to a considerably stronger carcinogenic influence than previous groups, so that we are led to the conclusion that this strengthening cannot have been effective before 1900, if the carcinogenic influence begins at the age between fifteen and twenty, although some increase in the intensity of the influence will have taken place both before and after the end of the century.

On the other hand, the birth groups of 1860 showed some increase in mortality from cancer of the lung before they arrived at the age of 75, so that under the assumption of a period of exposure of about 20 or 25 years, the latter cannot have begun later than about 1910.

It follows from these deliberations that if we assume an earlier or later beginning of the full exposure than the age between 15 and 20, we must respectively prolong or shorten the assumed period of exposure with a corresponding number of years, and allowance must be made for wide individual deviations either way. But with these reservations it seems reasonable to assume that the *minimal* average period from the beginning of exposure to the carcinogen till the death of the patient from cancer of the lung, will be about twenty years in Copenhagen, and that a strong increase in carcinogenic influence took place between 1900 and 1910.

The considerable length of the period of exposure would explain why we may now find the same exposure to a carcinogen for men and women, or for urban and rural areas, while their incidence of bronchial cancer still differs, in consequence of delays in exposure taking place decades ago.

PROGNOSIS OF THE INCREASE IN CASES

It follows from earlier parts of this paper, that the increase in incidence of bronchial carcinoma must continue until the curve for the birth groups at the highest level, as given in fig. X, has traversed the diagram, i. e. until all age groups of the population consist of persons which have been exposed to the carcinogen *ad maximum*. We can therefore compute the future mortality — or rather the approximate incidence — of cancer of the lung in Copenhagen, under the conservative assumptions that birth group 1905 represents the maximum exposure possible, and that the present age distribution of the male population remains. If described in terms of fig. X, the computation has been made on the basis of a curve representing the average shape of the curves for the various birth groups, and running at the level of birth group 1905, i. e. as a prolongation of the latter, so that the final level for all men will be reached in 1990 when the members of this birth group reach the age of 85.

Table II.
Cancer of Lung, Copenhagen.

Computed annual number of deaths:	
1951—55:	241
1956—60:	362
1961—65:	507
1966—70:	660
1971—75:	808
1976—80:	919
1981—85:	979
1986—90:	1007

In 1950 the total for cancer deaths among men in Copenhagen numbered 852, of which 168 were ascribed to cancer of the lung. In 1990 the number for the latter category alone will amount to about 1000, if therapeutic results remain the same. We

have every reason to expect a corresponding development, with a delay of about one decade, for provincial towns and rural areas, while the figures for women may show even a considerable further delay. For all we know, the prevention of a continued increase in deaths from bronchial carcinoma therefore equals in importance the effort against all other malignant diseases taken together.

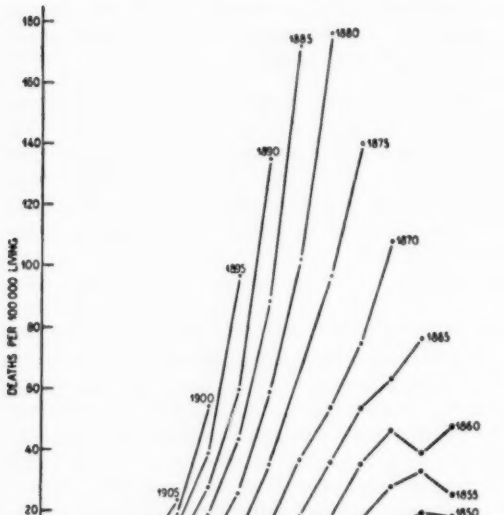


Fig. XIII.
Kennaway & Waller: Mortality from lung cancer in England-Wales.
Males. Groups born around year indicated.

It appears from the material available from other countries (21) that even if some of them may show present differences from Denmark, as for instance Iceland, where the increase in cases has not yet begun, or Norway, where it is still of limited extent, the principles in the development to date are probably the same, and there is no reason to doubt that its prognosis will appear as unfortunate, when calculated.

ETIOLOGICAL FACTORS

Bronchial carcinoma may be caused by the breathing of radioactive gas or dust, as in mines or in uranium refineries. It shows increased frequency among workers employed in certain nickel refineries, or exposed to chromates, isopropylic oil, iron dust and asbestos (12, 13, 21). Also workers in gasworks (8) or occupied with gas generators show an increased frequency of this disease, but, apart from miners in the Schneeberg and Jachymow districts, not even workers specifically exposed develop it with a frequency to explain the terrifying increase of rates observed for general male populations during the last decades. Radioactivity in the air is, to date, not of any significant magnitude in this respect.

In 1940, F. H. Müller (26) reported that on interviewing a number of patients with bronchial carcinoma about their habits, he had found that many were heavy smokers and he made a systematic inquiry, the results of which suggested a connection between bronchial carcinoma and tobacco smoking. From 1950 and later, a number of similar investigations have been reported, particularly from England and the U. S. A. (2, 7, 9, 19, 22, 23, 24, 27, 28, 34) comprising a total of about four to five thousand patients with bronchial carcinoma and a corresponding number of control persons, either normal or suffering from other diseases. A review, with tables in English, giving the basic figures from all these inquiries has previously been published from this institute (6) and only a few special features, which often pass unnoticed, will be mentioned here.

Briefly stated, the inquiries show a higher number of heavy smokers among patients with bronchial carcinoma than among the control persons, and the differences seem more striking the larger the number of persons questioned are. However, since there a number of non-smokers with bronchial carcinoma, and i larger number of smokers without the disease, the figures often fail to convince lay readers accustomed to the more striking figures from studies in infectious disease.

In this connection it may be pointed out that information on smoking habits must be of limited accuracy, when it is a question of decades. Furthermore, in most statistics the category of »mixed smokers« have made it necessary to express the consumption of cigars and smoking tobacco as the »equivalent« number of cigarettes, which must be done more or less arbitrarily as long as the character of the carcinogenic compound is unknown. It is interesting that one of the clearest studies is reported from a Finnish population (19) in which smokers used almost exclusively cigarettes.

Even if inaccuracies in figures may tend to obscure the difference in incidence of bronchial carcinoma between heavy-smokers, light-smokers and non-smokers, there may still be important factors deciding whether exposure to tobacco smoke will result in provocation of bronchial carcinoma. Doll and Hill (7, 9, 21), in their exemplary study of nearly 1500 patients and a corresponding number of controls, besides demonstrating beyond doubt an association between bronchial carcinoma and tobacco smoking, investigated the significance of a number of secondary factors. It seems particularly interesting that the percentage of smokers which said they inhaled, was practically the same among patients and controls. However, it was found that the percentage of smokers who said they never inhaled was lower

for patients with growths situated in periferal bronchi than among patients with central growths. Thus, it seems that the carcinogen reaches the main bronchi irrespective of conscious inhalation, and that the latter will extend the influence of smoking to wider areas of the bronchi.

Sadowsky, Gilliam and Cornfield (27) interviewed patients with cancer of lip, tongue, oral cavity, pharynx, esophagus, larynx and lung. The authors found an association between pipe smoking and cancer of the lip, cigar- or pipe smoking and cancer of the tongue, and between cigarette smoking and cancer of larynx, oesophagus and lung. Levin et al. (22) found similar associations for pipe smoking and cancer of the lip, and cigarette smoking and cancer of the lung. These results might suggest that the closer to the lip combustion takes place, the further down respiratory passages will a carcinoma develop, as if the carcinogen distills into the body to deposit at a certain temperature.

Observations of this kind can only be explained through direct determination of the chemical character of the carcinogenic agent or agents. It is therefore important that Wynder et al. (35) have been able to produce skin carcinoma in mice regularly by means of a solution in acetone of condensate of cigarette smoke. This technique may be the means of an effective search for those compounds that are carcinogenic in man, but as pointed out by the authors, it amounts to no proof of the part played by tobacco smoke in the etiology of bronchial carcinoma in man. Carcinogens may be active in one kind of animal, if applied to its skin, but inactive to other strains of the same species, and even to other tissue in the same individual. The academic proof of the carcinogenic quality of tobacco smoke, claimed so eagerly for all but academic reasons, may therefore only be produced by removal of the suspect agent from fifty per cent of a population previously exposed, followed by the disappearance — complete or partial — of the disease from the same fifty per cent. There are many examples, also from the field of cancer, that a chain of causal factors, imperfectly known, was broken by elimination of one of its links, so that the prevention of the disease finally established a suspected etiology.

PREVENTION

It seems impossible to escape the conclusion from the studies reported that we are now facing the beginning of one of the major catastrophes in medical history. A mortal disease, which demands decades for its development, and probably as lengthy efforts for its prevention, is now rapidly increasing because of widespread addiction beyond reason, economics and pleasure to a Red Indian habit, harmless if administered with sense. The real extent of this catastrophe is hitherto only realized by a limited number of workers, most of which consider their duty as done, when they have warned a public warned every day against — isms, insect poisons and hydrogen bombs. However, neither the duty of medical men, nor prevention of disease was ever finished with warnings in the presence of avoidable mortal disease increasing on the scale of a pandemic.

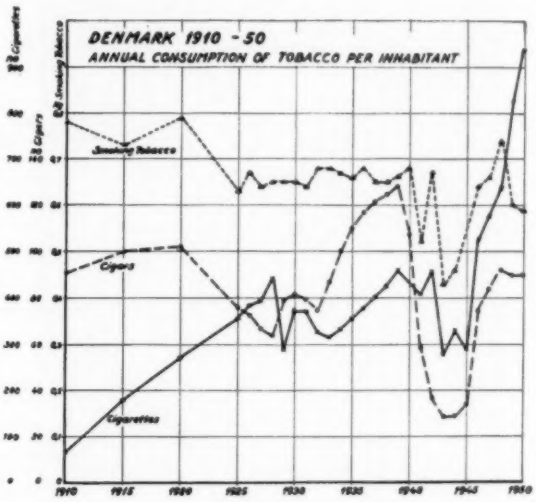


Fig. XIV.

Annual consumption of tobacco in Denmark 1910 to 1950 stated as number of cigarettes or cigars and kilograms of smoking tobacco per inhabitant.

First of all, the younger generation must be prevented from adopting the exaggerated smoking habits of the present generation. The earlier the exposure the heavier the risk, even up to the oldest age, and the earlier the warning the greater the chance of its success.

It will also be within the power of authorities in all countries to enforce filter-tips on cigarettes, and there is every reason to believe that this will reduce the heavy toll of lives ahead. It is true that we have no guaranty of the effect until we known the chemical nature of the carcinogen, or further experiments are carried out, but we cannot wait, while men are dying by the thousands. Where were the guaranties in the combat against epidemics in the past? Let no one believe that the attitude of the public will remain indifferent to us now responsible, when in one or two decades the extension of the catastrophe will become apparent to everyone.

Videant consules — — —

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COARCTATION OF THE PULMONARY ARTERY

By TYGE SØNDERGAARD

The etiology of coarctation of the aorta of the adult type is unknown. Of several explanations the scodaic theory is the most widely accepted. This theory assumes that an extension of the tissue of the ductus arteriosus into the aortic wall contracts as the ductus undergoes obliteration. And it has been shown that in cases of coarctation of the aorta the middle elastic layer of the aorta is largely replaced by muscular tissue similar to that in the wall of the ductus.

Against this theory has been held that »the pulmonary artery is never constricted in the process of involution of the ductus« (B r o w n, 1950).

Recently we have seen three patients with congenital heart disease and a constriction of the pulmonary artery where this vessel is joined by the remnants of the ductus arteriosus — a condition, which in analogy with the well known constriction occuring at the other end of the duct must be called »Coarctatio arteriae pulmonalis«.

From the Surgical Department L, Kommunehospitalet, University of Århus (Head: *N. Blixenkrone-Møller)* and Surgical Department D., Rigshospitalet. University of Copenhagen (Head: *E. Husfeldt).*

CASE REPORTS

Case 1: A four year old boy (RH Ped. Dept. 697/52) with history and findings typical of a severe Tetralogy of Steno-Fallot. Surgical treatment was recommended and August 22, 1952 an anastomosis between the left subclavian artery and the left pulmonary artery was performed (Surgeon: F r. T h e r k e l s e n).

The main stem of the pulmonary artery was normal close to the heart but markedly constricted at the bifurcation. The left branch of the pulmonary artery was also narrow in the first part, but the peripheral part was of a normal caliber. The right branch was not inspected.

The anatomical picture was so striking that the term coarctation of the pulmonary artery immediately was suggested.

Several times during the operation there was a drop in blood pressure and weak contractions of the heart, but the child recovered every time as soon as the left lung was reexpanded.

At a follow-up examination in September 1953 he was found very much improved. He had a continuous murmur as a sign of a functioning anastomosis.

Case 2: Boy, 10 months old. (A.K.H. Surg. Dept. L. 1094/53). Shortly after birth he became cyanosed and short of breath. He had been unable to gain weight in the last two months.

The physical examination, X-Ray of the heart, ECG and laboratory determinations were typical of a severe Tetralogy of Steno-Fallot and he was operated upon February 24, 1953. (Surgeon: T. S.).

A high infundibular pulmonary stenosis was found, but also a constriction of the right, the left and the main pulmonary artery at the point of bifurcation, and this point was definitely pulled towards the aorta by the ligamentum arteriosum. The left branch of the pulmonary artery was normal in the hilum of the lung, but contained a glistening white body anchored to the inside of the wall of the artery by a short fibrotic band (B in Fig. 2). When the artery was opened this body was pulled out and an anastomosis between the left subclavian artery and the left pulmonary artery was performed according to B l a l o c k.

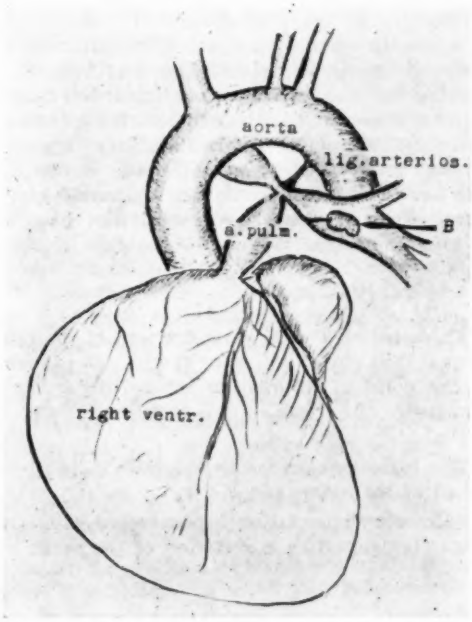

Fig. 1.
Conditions in case 2. B: The body in the left branch of the pulmonary artery.

The body measured 5×4×3 mm (Fig. 2) and consisted of a soft central part surrounded by a dense fibrous membrane in most places covered by endothelium (Fig. 3). Biochemical analysis revealed calcium phosphate, cholesterol and protein.

During the operation it was discovered that the slightest traction on the left pulmonary artery caused a falling blood pressure and depression of the heart action.

In August 1953 he was much improved with only minimal cyanosis.

Case 3: Female, 29 years old. (A.K.H. Surg. Dept. L. 694/54). Since early childhood palpitations and shortness of breath during exercise. The last year she had been slightly but permanently cyanosed. Cardiac catheterization disclosed an atrial septal defect and a valvular pulmonary stenosis with a pressure of 150 mm of mercury in the right ventricle. Surgical treatment was recommended and she was operated upon February 3, 1954 (Surgeon: T. S.).

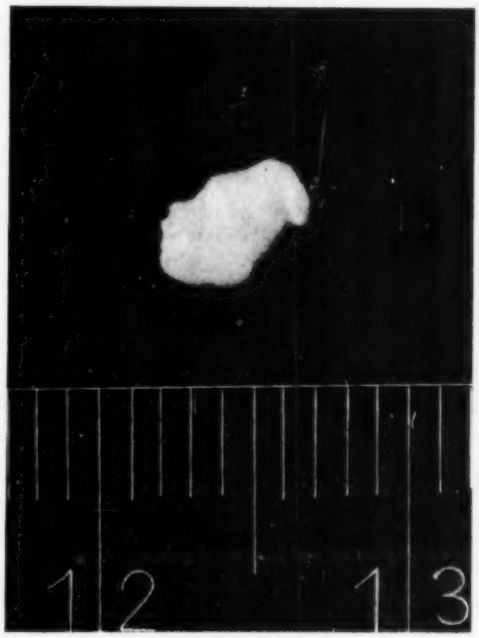

Fig. 2.
The white glistening body from the left branch of the pulmonary artery (scale in millimeters).

The pulmonary artery was only slightly dilated (in marked contrast to the »normal« poststenotic dilatation seen in these patients). At the point of division the main stem, and the right and the left branch of the pulmonary artery were constricted to a diameter of

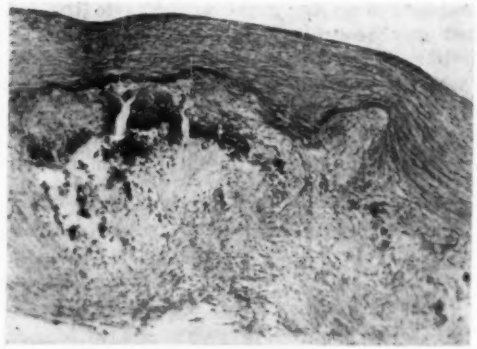

Fig. 3.
The soft central part and the fibrous membrane. Enlarged 108 x.

less than half the diameter of the left branch in the hilum of the lung. The region was carefully dissected and the arterial wall was found to be thickened in the constricted part, most marked where the ligamentum arteriosum joined the artery. Fibrous bands from the ligament were seen to bifurcate and loop around the right and left branch of the artery. (Fig. 4).

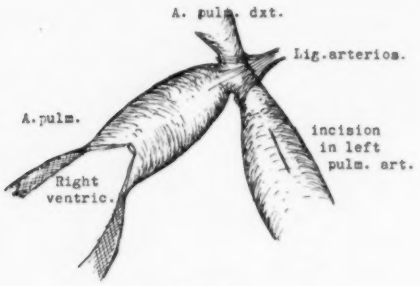

Fig. 4.
Conditions found in case 3. A very similar picture was recorded in case 1.

The ring clamp was placed on the left branch of the pulmonary artery and the valvulotomy was performed through this vessel (Søndergaard 1953). After the procedure the pressure in the right ventricle was 50 mm of mercury.

The patient was discharged the fifteenth postoperative day without cyanosis and much less shortnees of breath.

DISCUSSION

Schumacker & Lurie (1953) have recently reported a similar case: A 14-year old girl with a stenotic lesion at the bifurcation of the pulmonary artery. The etiology was not discussed.

Coarctation of the pulmonary artery must be considered a much more serious condition to the patient than coarctation of the aorta. It is naturally only compatible with life if the constriction allows sufficient blood to pass through to the lungs. There is no collateral circulation (except through a ventricular septal defect to the aorta and via the bronchial arteries to the lungs) while in the aortic system collaterals are available. All the blood from the right ventricle to the lungs must pass the stricture. In coarctation of the aorta the blood flow to the upper part of the body is normal.

In the aorta the pressure and the structure of the arterial wall tends to minimize the effect of constricting forces, but in the pulmonary artery the pressure is low and the wall is thin with very little resistance.

As the ductus arteriosus is able to close functionally in less than one minute, it can be assumed that muscular spasm plays some part in the closure. If an extension of the muscular fibres from the duct into the wall of the pulmonary artery is present, it is possible that a spasm of these fibres is able to close the pulmonary artery and cause the death of the infant. This condition can only be suspected if histologic examination demonstrates muscular tissue in the pulmonary artery similar to that in the wall of the ductus arteriosus. The spasm has disappeared at the time of post mortem examination.

It is important to recognize this condition during the operation, because the slightest traction on one branch of the pulmonary artery will produce a sharp angle between the main stem and the other branch of the artery and block the circulation to the lung. This was the case in the first two patients.

The last three years we have opened the pericardium in all cases of congenital heart disease in order to obtain maximal information about the malformations present. This has been done because the rapid developments in cardiovascular surgery makes it possible, that at least some of these patients will benefit from new types of surgical procedures. In many thoracic clinics this has not been done routinely, and undoubtedly many cases of pulmonary coarctation have remained undetected.

SUMMARY

Three patients with a constriction of the main stem of the pulmonary artery and of both branches at the point of bifurcation where the artery is joined by the ligamentum arteriosum, are reported.

The logical name for this condition is *Coarctation of the Pulmonary Artery.*

Pulmonary coarctation is considered more serious to patients than coarctation of the aorta.

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INVESTIGATION OF THE PROTEIN FRACTIONS IN THE CEREBRO-SPINAL FLUID BY ULTRACENTRIFUGAL ANALYSIS

By ESTHER FRANTZEN, ALLAN FRANTZEN, ROBERT JENSEN and TORBEN FOG

The more recent physico-chemical methods of protein analysis, which have been of great significance in the investigation of the protein fractions of the serum, have also been employed in recent years in the investigations of proteins in the cerebro-spinal fluid. The electrophoretic method may be specially mentioned in this connection. The findings hereby obtained have been employed to illustrate the question of the formation and resorption of the cerebro-spinal fluid (CSF) and the state of exchance conditions of the blood-fluid barrier under normal and pathological conditions.

Firstly, it was investigated whether the proteins in the CSF are the same as those found in blood. Secondly, attempts were made to determine the albumin: globulin ratio and compare this with that of the blood. Thirdly, the question was examined whether displacements in the serum proteins in pathological conditions are reflected in the CSF and cause displacements in its protein composition. Finally, an attempt has been made to utilize the findings diagnostically by investigating characteristic changes in protein fractions in various pathological conditions.

On account of the low protein content in the CSF, it is desirable, before electrophoretic investigations, to bring the protein contents up to approximately 1 per cent by preliminary concentration. To obtain this concentration, various methods have been employed, viz. precipitation, freeze-drying or dialysis.

Already in 1942, Kabat and co-workers (6) published investigations in which they concentrated the CSF by pressure dialysis and thereafter examined the fractions in Tiselius' electrophoresis apparatus.

Kabat and co-workers (5) later investigated the protein in the CSF by immuno-chemical methods, preparing antibodies partly against albumin and partly against γ-globulin and undertaking quantitative precipitation.

Ewerbeck (4) concentrated CSF by dialysis against a concentrated colloid or by ultrafiltration. The concentrate was investigated in a micro-electrophoresis apparatus.

Labhart and co-workers (7) concentrated CSF by pressure dialysis and thereafter analysed the concentrate in a similar apparatus.

Bücher and co-workers (2) precipitated the proteins of the CSF by acetone at low temperature and re-dissolved them in a lesser volume whereafter the analysis was undertaken by paper-electrophoresis.

Schneider and Wallenius (8) and Wallenius (9) concentrated CSF by dialysis against dextran in physiological saline. The concentrate was analysed by paper-electrophoresis. A similar technique was employed by Cumings (3).

These and other investigations, not mentioned here, have led to somewhat controversial results, although unanimity reigns on certain points. All investigators agree that in the CSF, the same protein fractions as known from the blood are encountered, viz. albumin, α-, β- and γ-globulins have been demonstrated. It must be mentioned that Bücher and co-workers (2) believe that they have demonstrated two constantly occuring small protein fractions in normal CSF which cannot be demonstrated in serum. This has not been confirmed by other investigators.

As regards the albumin:globulin ratio, some investigators (7) find that this is greatest in the CSF while others (9) find the same value in the serum and CSF under normal conditions. The majority of authors agree that diseases which produce displacements in the protein fractions in the serum, involve corresponding displacements in the CSF, only to a lesser extent. Thus, for example, in patients with cirrhosis of the liver with great increase of γ-globulin in the serum, a corresponding increase was found in the CSF without any symptoms being present indicating a disease in the central nervous system (9).

As regards disease in the central nervous system, the conditions in patients with acute and chronic infections, specially syphilis, and also with disseminated sclerosis and tumours have been particularly investigated. The findings are greatly diverging. A number of investigators found an increase of globulin, particularly γ-globulin, in syphilis and disseminated sclerosis (9) but definitely characteristic changes in certain diseases were not demonstrated.

While electrophoretic investigations of a protein solution express the state of electric charging of the individual protein fractions at the pH chosen, investigation by ultracentrifugation expresses the size of the molecules of the individual proteins.

Thus, a possibility is present of illustrating the question of the composition of the CSF from a new viewpoint. Investigations of the CSF by ultracentrifugal analysis have, to our knowledge, not been published previously. Only Brohult and

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Jensen (1) have undertaken some preliminary experiments.

The object of the present investigation is to elucidate to what extent ultracentrifugal analysis of CSF may contribute to solve some of the problems which, as mentioned in the introduction, are associated with the protein content of the CSF.

In the ultracentrifuge (abbreviated: UC) a small sample (see Figure I, shaded area in cell) about

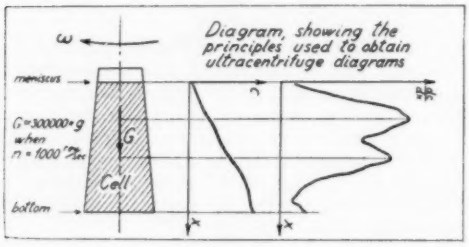

Fig. I.

1 ml of protein solution is centrifuged for some hours and (in the present series of experiments) at a speed of 1000 revolutions per second which corresponds to a centrifugal field, G, of nearly 300 000 g, where g is the field of gravity on the earth. In this enormously high centrifugal field the protein molecules in the solution will be centrifuged from the meniscus of the solution towards the bottom of the centrifuge cell. According to the size of the molecules they will move with different velocities. The construction of the ultracentrifuge makes possible a visual or photographic registration of this movement during the run, and so-called »ultracentrifuge-« or »sedimentation diagrams« can be plotted and »sedimentation constants« can be calculated from the diagrams. In the diagram the concentration gradient in the cell, $\frac{dc}{dx}$, is plotted photographically against the distance from the meniscus as abscissa by an optical »Schlieren« system. The example shown in the Figure (extreme right) is taken from an actual run of a protein solution 60 minutes after full speed was obtained. It is seen that the diagram has two peaks corresponding to two protein components. The lower one has moved further from the meniscus than the upper one which means that the molecular weight of the protein in the lower peak is greater than that in the upper one. The sedimentation is followed by a series of photographic exposures describing the state of sedimentation during the run of an experiment.

In the following Figures such series of exposures are reproduced. It has to be mentioned here that the diagrams are turned in such a way that sedimentation is proceeding in the direction from right to left. The optical system in an oil driven ultracentrifuge of the present type (Svedberg type) normally gives the best diagrams when protein concentration is about 1 per cent, but we have observed that the »Schlieren system« introduced in this ultracentrifuge by one of the authors (R. J.) in some cases has made possible a reliable observation of protein components present in concentrations less than 0.1 per cent. Under the different diagrams in the following Figures, the angle α of the inclined slit in the optical system is given. The vertical magnification of the diagrams are proportional to tan α. The protein concentration of the single components is proportional to the area under the corresponding peaks.

THE AUTHORS' PERSONAL INVESTIGATIONS

The samples of CSF examined were obtained partly at lumbar puncture, partly at lumbar air-encephalography and at ventriculography. On all samples, cell counting was undertaken and the protein content determined by the turbidimetric method. A modification of Denis-Ayer's method was employed by which the protein is precipitated by sulpho-salicylic acid. Reading was undertaken in Hilger's photoelectric absorptiometer. The apparatus is standardized by means of a serum dilution, the protein content of which is determined by micro-Kjeldahl analysis.

The remainder of the CSF sample was centrifuged immediately at 3000 revolutions per minute to remove the cells. The supernatant fluid was preserved in a refrigerator and examined in the ultracentrifuge after the shortest possible interval. No preserving agents were added. The content of erythrocytes in the CSF samples did not exceed 150 per cmm in any case which implies that admixing with blood in the samples of CSF examined was negligible. (In only one case, CSF 44, see later, no cell count has been made. At any rate, however, there was no visible blood contamination).

I. Experiments with Concentrated CSF.

In the first series of experiments, we concentrated the samples of CSF prior to investigation in the ultracentrifuge. Experiments were performed with two different methods of concentration. In the former, CSF was dialysed first against psysiological saline and thereafter against 20 per cent dextran saline. After the eclapse of approximately 3 days, the greater part of the water content of the CSF has diffused out and the content of the bag is reduced to some few ml with a correspondingly higher protein content. A similar method was employed by Wallenius (9), among others, prior to electrophoretic experiments. In some of our experiments, we determined the nitrogen content by micro-Kjeldahl analysis, as well following dialysis against saline as on the concentrate after dialysis against dextran saline. These determinations together with measurements of the reduction in fluid volume during dextran concentration showed that during this

concentration, a loss of protein occurs which may be about 30 per cent. In the latter method of concentration, we dialysed CSF first against a saline solution corresponding to 1/10 or 1/20 physiological saline solution. Distilled water was not employed as this would involve precipitation of part of the globulins. After dialysis, the fluid was freeze-dried and the dry material re-dissolved in

Figure II shows the results of the UC experiments. The upper row of pictures shows the experiments in which the CSF was introduced directly into the cell without any preliminary concentration. It appears, that with a protein content of 0.2 per cent, a »Schlieren« picture of reasonablye good quality may be obtained when a suitable enlargement is employed. The distinctness

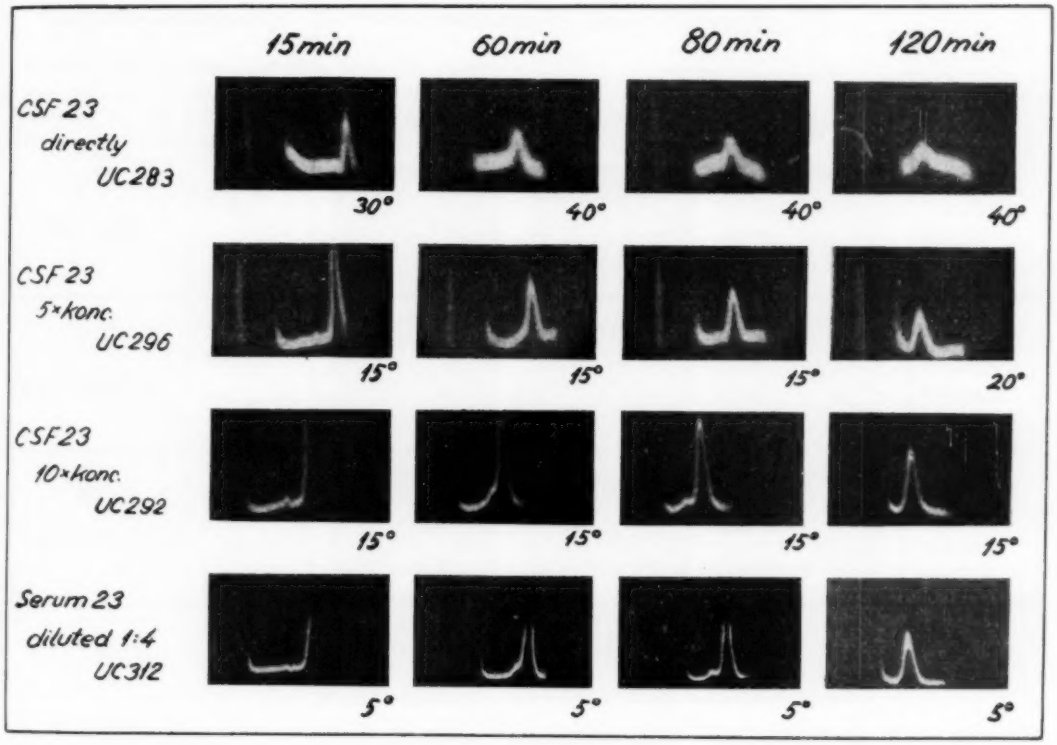

Fig. II.
Sedimentation diagrams of the cerebro-spinal fluid (CSF 23) and the serum from the same patient.

1/10 or 1/20 of the original volume of distilled water to achieve a final salt concentration corresponding to physiological saline. With this method of concentration, loss of protein occurs also, which will be mentioned under the description of the experiments.

In the first experiment, to be recorded, we chose to investigate a sample of CSF, the protein content of which was so high that it could be assumed in advance that is was possible, as a control, to investigate it also in the unconcentrated condition.

This specimen, CSF 23, originates from a male, aged 37 years, who had suffered from an intermittent discharge of CSF via the nose for two years, presumably as a result of a skull injury. The sample was obtained at lumbar air-encephalography which showed pronounced brain atrophy. The cell count was 2/3 white cells and 350/3 red cells and the protein content was 200 mg per cent.

of the curves suffers, however, somewhat by this enlargement. The following two rows show experiments with the same CSF, concentrated by freeze-drying. It was concentrated 10 times and the corresponding experiment appears in the third row. In the second row, the concentrate was diluted to double volume (thus corresponding to concentration 5 times). For comparison, we have recorded the diagrams for the serum of the same patient, diluted 1 : 4 with 0.2 molar NaCl, in the lowest row. The diagrams show immediate similarity between serum and cerebro-spinal fluid. The first vertical column of the diagrams is recorded 15 minutes after the UC had achieved its maximum speed. In these pictures, the so-called 20 S-component appears as a small peak before (to the left of) the albumin-globulin peak. In the next column, which shows the diagrams photographed after 60 minutes, the globulin peak is about to separate from the albumin peak, and

after 80 minutes it is clear of this. After 120 minutes, the globulin peak has moved to the bottom of the centrifuge cell and only the albumin peak is visible.

Figure III shows experiments with 3 samples of CSF, all of which were concentrated by freeze-drying. The upper row corresponds to the experiment shown in Figure II (10 times concentrated CSF). This is tabulated together with 2 other samples of CSF both with originally normal protein content, but concentrated 20 times.

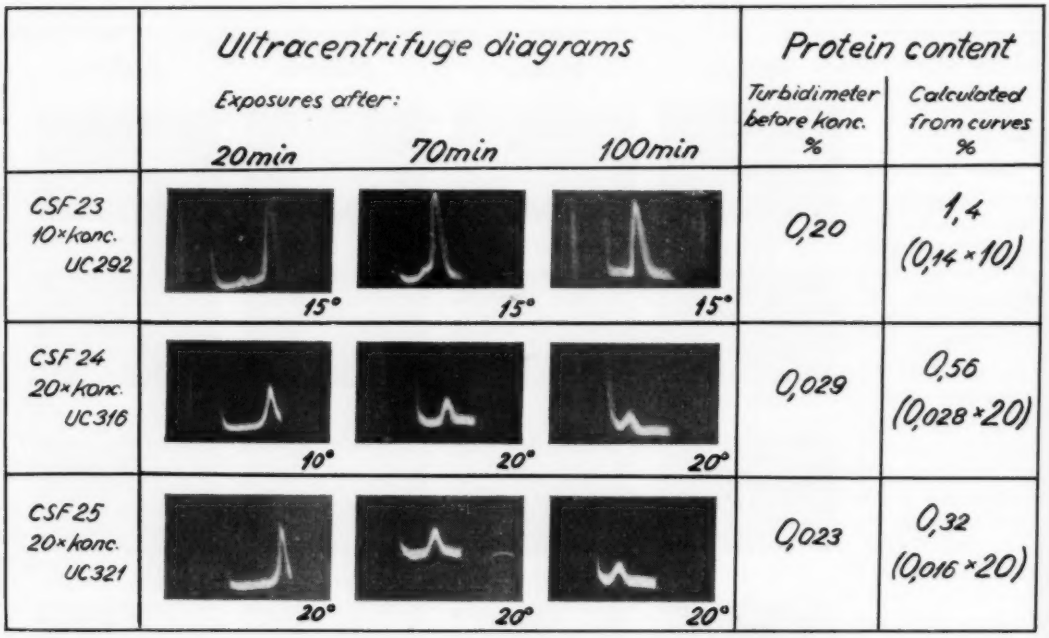

Fig. III.
Sedimentation diagrams of three CSF concentrated by freeze-drying.

CSF 24 comes from a female, aged 44 years, with trigeminal neuralgia. The sample was obtained at lumbar air-encephalography which showed moderate diffuse atrophy of the brain. The cell count was 1/3 white and no red cells per cmm; the protein content was 29 mg per cent.

CSF 25 comes from a female, aged 20 yars, suffering from the sequelae of a skull injury. The sample was obtained at lumbar air-encephalography which showed slight diffuse atrophy of the brain. The cell count was 3/ white and few red blood cells per cmm; the protein content was 23 mg per cent.

Here also, the 20 S-component is discernible in the first column while the globulin peak is just visible in the following column. The albumin peak is very distinct in all 3 columns.

As mentioned previously, the area below the peaks corresponds to the protein concentration. In the last column in Figure III, the protein concentration is calculated in this way while the next to last column records the results of the anticipated to 2 per cent but only to 1.4 per cent. Micro-Kjeldahl analysis of the 10 times concentrated CSF 23 revealed 1.34 per cent protein. A loss of protein thus took place, the cause of which, however, we are unable to completely explain.

While the albumin peak is distinct in these diagrams, the globulin peak is so feebly marked that a quantitative calculation of the relative globulin content cannot be carried out.

II. Experiments with Unconcentrated CSF.

Figure IV shows experiments with 3 samples of CSF with pathologically increased protein contents. For comparison, the sera of the same patients were also investigated.

CSF 42 comes from a male, aged 56, suffering from a malignant meningeoma of the wing of the sphenoid, recurring after operation. The sample was obtained at ventriculography. The cell count was 2/3 white and 160/red blood cells per cmm. The protein contens was greater than 200 mg per cent (turbidimetric).

CSF 44 was taken from a female, aged 66 years, suffering from intracerebral metastasis from a bron-

chial carcinoma. The sample was obtained at lumbar puncture. No information concerning cell counts is available while the protein content was 166 mg per cent.

CSF 45 comes from a female, aged 59 years, suffering from a neurinoma of the acoustic nerve. The sample was obtained at ventriculography. The cell count was 2/3 white and 76/3 red blood cells per cmm. The protein content was greater than 200 mg per cent.

After 20 minutes the 20 S-component appears in all three CSF samples; after 80 minutes, the globulin component separates from the albumin peak and after 120 minutes, only the albumin peak remains in the diagram. The sedimentation pictures are thus uniform for the three CSF samples in these cases. Comparison with the corresponding serum diagrams shows that CSF contains the same protein fractions which can be demonstrated in the serum. The quantitative ratios between fractions does not show any striking deviations from the conditions in the corresponding sera either.

CSF 46 and 47 come from a male, aged 47 years, suffering from an acute meningo-myelitis. The samples were obtained at lumbar punctures with an interval of a month between. The pressure conditions were normal without block; the cell counts were 243/3 and 202/3 white blood cells (lymphocytes); no red

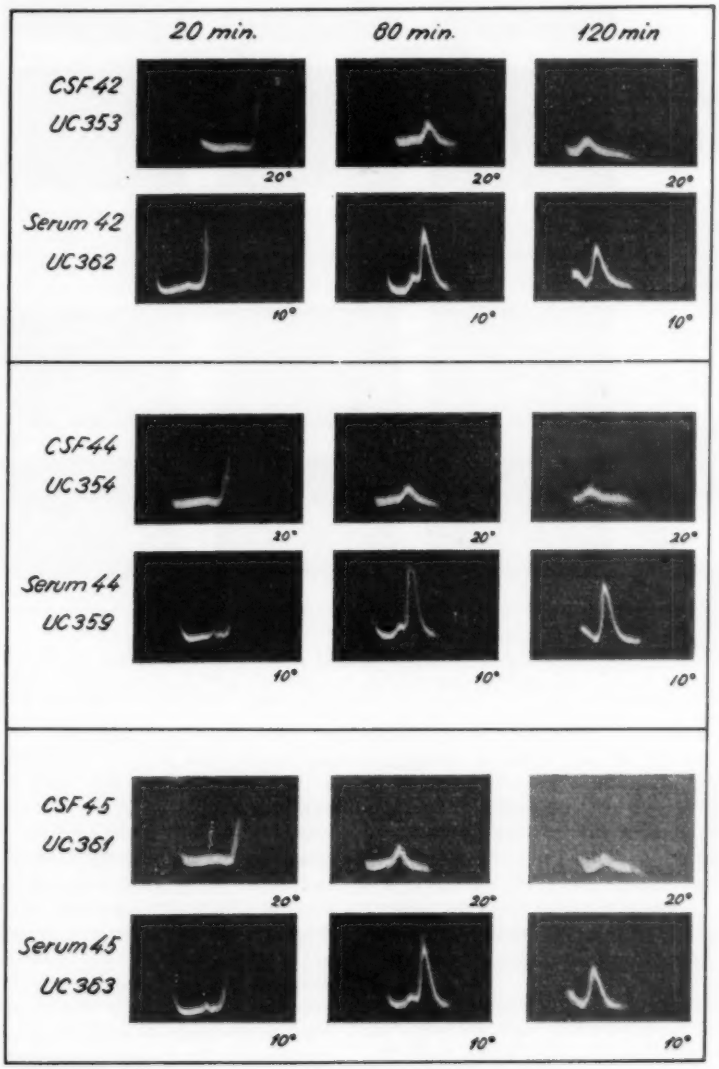

Fig. IV.
Sedimentation diagrams of three unconcentrated CSF with high protein content and sera from the same three patients.

cells. The protein contents were 90 and 118 mg per cent. The patient is a diabetic.

Simultaneously the serum was examined. The results appear in Figure V. In this case it appears that the UC diagram for CSF deviates substantially from the diagrams shown previously. After 80 minutes, it appears that the globulin peak (to the left in the diagram) is unusually large, nearly as large as the albumin peak (to the right in the diagram). No corresponding displacement in favour of the globulin fraction can be demonstrated in the patient's serum, as appears in Figure V. The same displacement of the protein fractions in the CSF was observed in the second set of samples taken from the patient after the lapse of one month and examined in the same way, as appears in the two lower rows in the Figure.

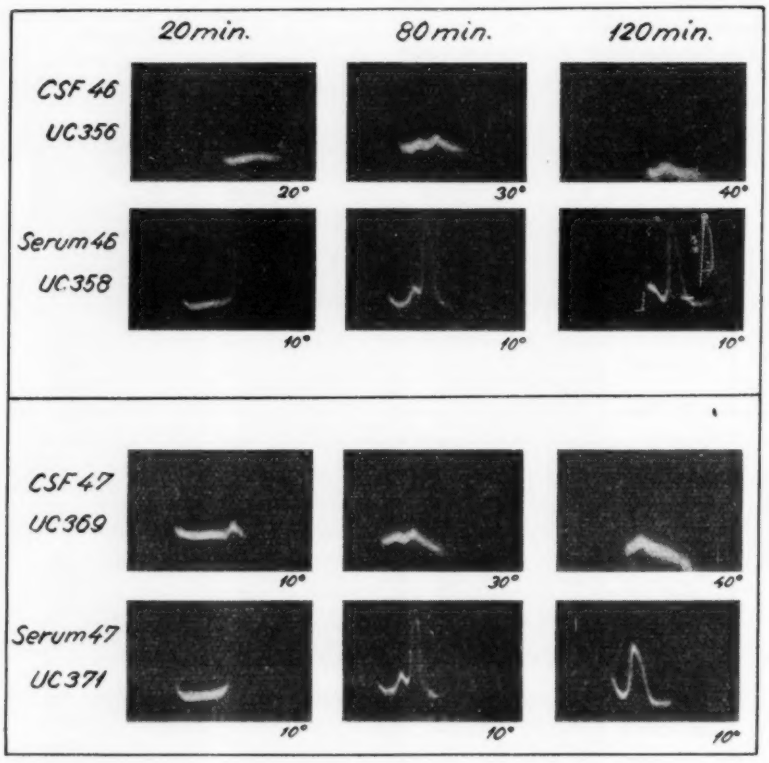

Fig. V.
Sedimentation diagrams of CSF and the corresponding serum both taken at two occasions with a time interval of one month.

In addition to the above mentioned we investigated 7 CSF samples from patients with various neurological diseases. All of them show UC diagrams which correspond to those recorded in Figures II—IV, in which the albumin peak is predominant and the globulin peak is only feebly marked. This holds true also for a sample from a patient with diabetic polyneuritis (protein content 108 mg per cent).

DISCUSSION

One of the advantages of the modern methods of protein analysis, electrophoresis and ultracentrifugation, is that the protein substances may be investigated in their native condition. As in normal CSF only about 0.03 per cent (0.02—0.04 per cent) total protein is present, greater differentiating ability of the optical system in these apparatus than hitherto normally employed, is required if the protein content of normal CSF has to be analysed. Concentration of the CSF samples is another alternative, but it must be required that such a concentration does not involve loss or denaturation of the native proteins.

Previous authors have not satisfactorily accounted for the extent to which their methods of concentration have involved loss of protein. If such a loss occurs, as is demonstrated in our experiments, it is not a priori allowed to assume that the loss involves all protein components to an equal extent. In this way, the results may be distorted.

Another glance at Figure II makes it apparent,

however, that none of the components (20 S-component, the globulin and albumin components) which are present in the untreated CSF disappeared on concentration. It is therefore improbable that the loss of protein observed affected only a single protein fraction while, on the other hand, particularly the globulin peaks are so diffusely delimited in the present diagrams that, at present, we have not been able to make a reliable quantitative calculation of the distribution of the protein loss in the isolated fractions. We have therefore proceeded to investigate CSF samples with increased protein content, which may be examined without preliminary concentration. We have thus been forced to refrain from investigating normal CSF samples. On the other hand, we have, in this way, ensured that the present diagrams with great probability record the protein fractions in their native condition in the pathological samples of CSF examined.

It appears from the UC diagrams recorded, that the CSF contains qualitatively the same protein fractions as does the serum. It may be added that the sedimentation constants found correspond to those familiar from investigations of serum proteins. In the majority of investigations, the albumin fraction was the dominant fraction. In one patient (see Figure V), a relative increase of the globulin fraction was found. This finding could be reproduced after the lapse of one month and it was not accompanied by displacement in the serum protein fractions.

The results of a more quantitative treatment of the findings mentioned in the present paper will be recorded elsewhere in the near future.

SUMMARY

A number of samples of cerebrospinal fluid from patients with various neurological conditions were examined by ultracentrifugal analysis. The majority were examined without preliminary concentration. It is pointed out that such concentration may involve loss of protein. It is demonstrated that the same protein fractions as those with which we are familiar in serum may be demonstrated qualitatively in the CSF.

In one patient, a relative increase of globulin without simultaneous displacement in the serum protein fractions was encountered.

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JUDET's ARTHRO-PLASTIC HIP JOINT OPERATION

COMPARATIVE PRESSURE TESTS WITH A NEW ANGLED PROSTHESIS

By R. MOVIN

Having reviewed over 200 arthro-plastic hip-operations we feel justified in raising the following objections to Judet's method.

1. The Judet prosthesis is supported wholly by cancellous bone.
2. The deep and narrow circular groove under the head of the Judet prosthesis encloses cancellous bone, and there is some risk of impairment of the blood supply to this enclosed tissue.
3. The stem of the Judet prosthesis is fixed directly in the neck of the femur in its own line of axis, whereas, from a mechanical point of view, a steeply placed stem affords greater strength.
4. The Judet prosthesis is not considered fit for cases of transcervical fractures of the neck of the femur, especially not in cases of lateral fractures and in old cases with necrosis of the head and the neck of the bone.
5. The acrylic material used is not resistant to wear.

From the Orthopaedic Hospital, Copenhagen. Department I (Senior Surgeon: *Arne Bertelsen*).

The operations under review have been carried out since May, 1951. Ten prostheses worked themselves loose, seven others are suspected of movement because of X-ray pictures showing pronounced wastage of the bone in the neck. In a prosthesis removed after two years we found about 2 mms corrosion of the acrylic material.

Therefore, we do not feel confident with regard to Judet's arthroplasty and have abandoned the method. From March 1953 we have designed and developed two new types of nylon-acrylic, angled prosthesis, which have been made in our own workshops in the Hospital.

Up to date we have carried out 53 operations using these new prostheses, so far with satisfactory results: 15 on newly admitted cases of transcervical fractures of the neck of the femur, 21 on cases having complications of this fracture, and 17 on cases suffering from osteoarthritis.

The main features in the two designs of the new prosthesis are:

1. The stem is steeply graded for it to rest on the calcar femorale medially, and to perforate the external cortex of the bone deeply laterally.
2. The supporting surface is horizontal in one design A. (fig. 1.) and nearly so in the other B. (fig. 2.)
3. In one type of the prosthesis (A) there is no groove (fig. 1) but the alternative design (B) has a small groove (2 mms) under the head. (fig. 2.)
4. The stem being steeply graded, the head had to be mounted medially at an angle of 45° in order to avoid luxation.
5. In order to reduce tissue reaction from dust caused by wear of the head, the head is made of nylon. According to tests carried out by the author nylon is more resistant to such wear. But even Nylon demonstrated considerable wear and the head of the prosthesis is now covered with a vitallium cup.
6. The supporting surface and the stem, is still made of the acrylic material in order that acrylic cement may be used to fix the prosthesis. (1, 2).
7. By backward rotation of the above mentioned types of prosthesis during fixation, the head of the prosthesis may be fixed in retroversion to avoid luxation in front. This is of importance especially in case of sub-luxation or luxation.

Both of the above mentioned prostheses may possibly meet the demands of efficiency, but the prosthesis A, incorporating the horizontal supporting surface, gives better conditions for securing pressure and stability, furthermore it has the advantage of being self-locking. Rotation is prevented, because the supporting surface is not at right angles to the stem, and the lateral part of the prosthesis is wedged firmly in the angle between the greater trochanter and the horizontal supporting surface of the bone. (fig. 4 & 5).

The major condition for a prosthesis to stand the weight bearing of the patient during the rest of his life is that the prosthesis at the time it is inserted fits correctly and will support the heavy weight and pressure to which it is subjected. Bearing this in mind, the following comparative pressure tests which have been undertaken may be of interest:

At post-mortem examinations of patients who had died from various causes, six were selected

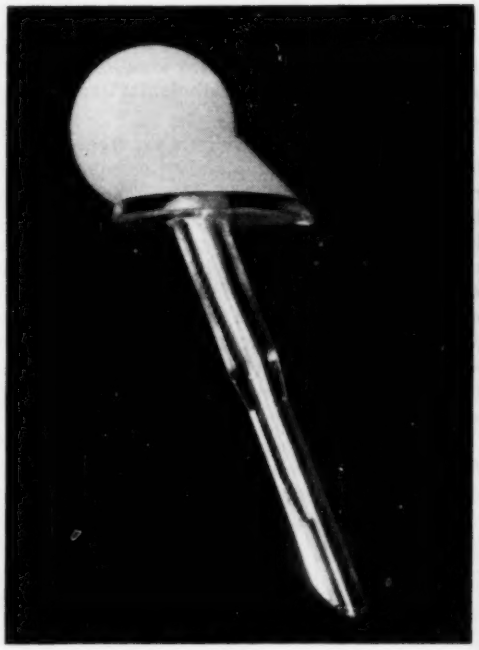

Fig. 1.
The new design of self-locking angled hip-prosthesis (A) with horizontal supporting surface.

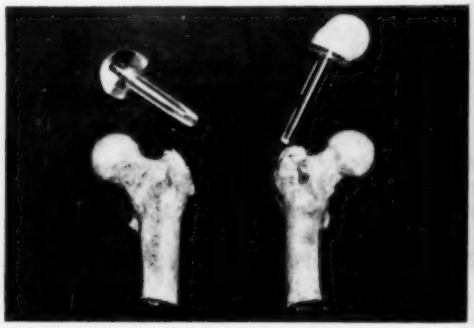

Fig. 2.
Femurs removed from the same individual, the left to be fitted with a Judet prosthesis, the right to be fitted with a angled prosthesis (B). A special reamer is used to adjust the bone for this design.

for the upper part of both femurs to be removed. These twelve femurs included six which had a Judet prosthesis and six which had the newer type fitted (fig. 2 & 3). These 'upper portions' of femurs were mounted in cement up to the level of the minor trochanter — in an iron canister — in such a manner that each was in the same position as in the patients' leg when standing. In this way one was able to exert varying pressures upon the head of each prosthesis inserted in the bone, and to see how each type of prosthesis tolerated these pressures, when imposed by a hydraulically operated press.

The results of these comparative tests showed that femurs fitted with the Judet prostheses were able to withstand on the average, a gradually increased pressure up to 467 kilos, whereas those fitted with the newer types of prostheses were able to withstand an average pressure of 1444 kilos.

As the femurs were operated on and tested by pressure within the first few days after the death of the patient and the bones were preserved in a solution of "Sanol" 1:50 the conditions were as "natural" as possible.

The most striking feature with regard to the femurs fitted with Judet prostheses was that two were only able to withstand pressures of 240 and 285 kilos respectively. The recorded pressures from the Judet-fitted femurs varied between 240 and 780 kilos, but the femurs which had been fitted with the new type prosthesis showed a much greater resistance and relatively less variation, ranging from 1250 to 1750 kilos.

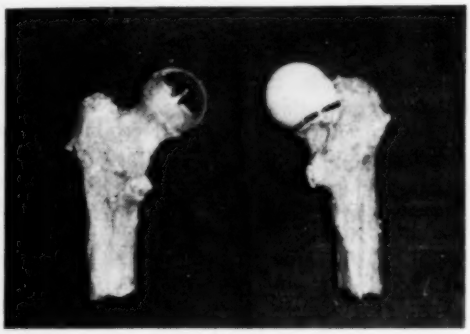

Fig. 3.

The femurs shown in fig. 2 with the prostheses mentioned in the illustration and ready for pressure tests when mounted in cement. Both stems are perforated through the external cortex as described and felt is placed over the perforation to prevent the stem from taking support from the surrounding cement during the pressure test.

In this case the Judet prosthesis supported 240 kilos and the angled prosthesis with the steeply placed stem (B) 1750 kilos.

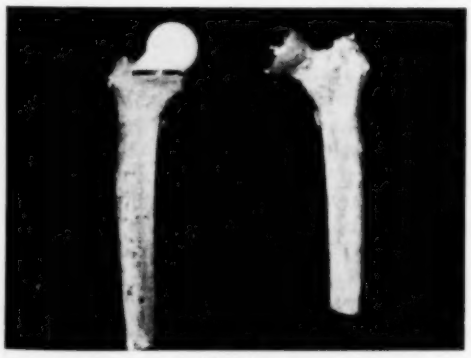

Fig. 4.

Femurs from the same individual, the left fitted with the prosthesis (A) shown in fig. 1, the right fitted with a Judet prosthesis.

The bone fitted with the Judet prosthesis supported 285 kilos, the bone fitted with the design A of the angled prosthesis 1390 kilos.

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Fig. 5.

X-ray of a patient suffering from osteo-arthritis of the hip joint. The new self-locking type of angled prosthesis (A) with horizontal supporting surface has been inserted. The outlines of the prosthesis are drawn up.

Note: The lateral part of the prosthesis has to be resected by a saw before insertion. The part to be resected varies from individual to individual depending on the size of the bone. The lateral part of the prosthesis is wedged firmly in the angle between the greater trochanter and the horizontal supporting surface of the bone and the stem is resting on the calcar medially.

BLOOD VOLUME DETERMINATION BY MEANS OF RADIOACTIVE PHOSPHATE

WITH SPECIAL REGARD TO CLINICAL APPLICATIONS

By HANS H. BOHR

SUMMARY OF THESIS

As described by Hahn and Hevesy (4), it is possible to use red blood corpuscles, labelled with P^{32}, for blood volume determinations. The present paper summarizes an investigation on this method, and the results obtained with it under various conditions (1).

THE METHOD

Originally red blood corpuscles were labelled *in vivo*. It was shown by Hevesy and Zerahn (5) however, and confirmed by several other authors, that red blood corpuscles labelled *in vitro* will only give off P^{32} at a rate of about 10 % pr. hour, when injected into the circulation. Reeve and Veall (7) proposed to separate the red blood corpuscles from the active plasma before injecting into the vein. The uptake and loss of P^{32} by erythrocytes has been investigated by the author in an earlier publication (2).

The technique preferred by the author is the following: Blood drawn from the patient is incubated at 37° C. with P^{32} for 1/2 hour. The red blood corpuscles are then separated from the plasma by centrifugation and washed several times with saline. A suspension of the blood corpuscles is injected intravenously, and after the lapse of 10—15 minutes, allowed for mixing in the circulation, blood samples are withdrawn. The blood samples are hemolysed with Saponin and filled into small cuvettes (8). The radioactivity is measured with a Geiger-Müller counter above and below the cuvette in an automatic sample changer. The activity A of the blood samples is compared with the activity B of the injected blood corpuscle suspension. If the amount of injected blood corpuscle suspension is M ml, the total blood volume V can be calculated from the equation $V = M \cdot \frac{A}{B}$; and the blood corpuscular volume from V and the hematocrit value.

The method was tested in different ways both in vitro and in vivo, showing an accuracy of about ± 3 %.

With the method of P^{32} as with any other method where the indicator is attached to the red blood corpuscles it is essentially the blood corpuscular volume, which is determined. It has been pointed out by several authors that these methods give a lower value for the blood volume than those methods where the indicator is attached to constituents of the plasma. This disagreement has been thought to be due to a different distribution of blood corpuscles and plasma in the large and the small vessels, giving a hematocrit value in the venous blood samples, which is higher than the "true hematocrit" of

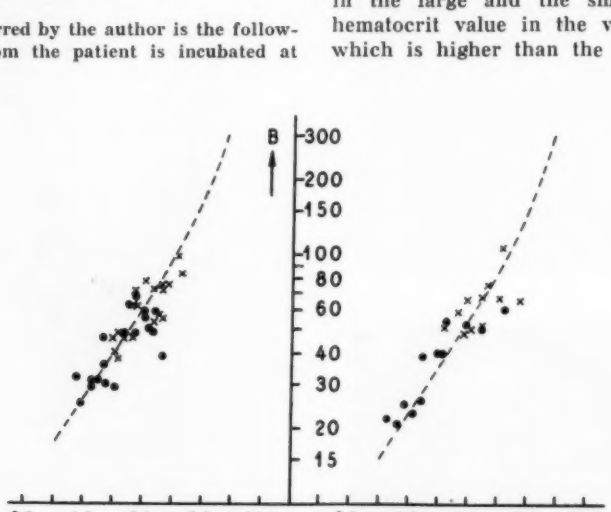

Fig. 1.

The figure shows the relation between the blood corpuscular volume pr. kg. bodyweight (B.) and the hematocrit value (H.) in patients with polycythemia vera, in a semilogarithmical scale. Crosses signify the values before treatment and circles the values after treatment with P^{32}. The figures for women are shown to the right, for men to the left. The dotted lines represent the relation between B. and H. when the plasma volume is constant, in women 35, and in men 40 ml. pr. kg. body weight.

all the blood in the body. A review of the results published does however show that the differences between the "true hematocrit" and that determined in the venous blood samples does not exceed 10 % and is often less than 5 %. In the opinion of the author a difference of this order may be introduced through the error due to ineffective centrifugation when determining the hematocrit. In the present investigations the hematocrit was determined by the method of v a n A l l e n. The centrifugation speed was 4000 rotations pr. min., with an effective radius of 15 cm. Under these conditions the amount of "trapped plasma" is below 3 % (6).

It may be mentioned that through determination of the blood corpuscular volume before and after exercise or a heavy meal the present investigation confirms the general view that no blood depots of importance exsist in the human body.

RESULTS OF BLOOD VOLUME DETERMINATIONS IN PATIENTS

I. The blood corpuscular volume and the hematocrit value was followed in 50 patients from the surgical departments of the University Hospital, Copenhagen. On 37 of these cases a gastric resection for duodenal or gastric ulcer was performed. The average values during the first two days following the operation showed an increase in the blood corpuscular volume by 6 % (including the blood transfusions given) and in the hematocrit value by 11 % compared with the values before the operation. This indicates that hemoconcentration had taken place. The blood volume measurements did however show variations with increases and decreases of as much as 40 %. In the opinion of the author this is due to deficient circulation which, according to previous investigations, may arise especially after laparotomies. As a consequence blood volume measurements under these circumstances must be controlled either by repeated measurements or by following the "mixing curve" for at least one hour.

II. Blood volume determinations were also carried out during the last month of pregnancy in a number of patients at the School of Midwifery. 16 measurements on 9 normal patients showed an average blood corpuscular volume of 1920 ml., which is about 18 % above the normal values for women, and a plasma volume of 3400 ml, or about 40 % above normal values.

III. Further, the blood volume has been determined in patients with polycythemia vera under treatment with radioactive phosphorus at the Finsen Hospital, Copenhagen. The results of the measurements before treatment showed an average blood corpuscular volume in women of 3760 ml. or 63 ml. pr. kg. body weight, with a mean hematocrit of 64. Measurements in 20 men showed a blood corpuscular volume of 4170 ml. or 59 ml. pr. kg. body weight, with a mean hematocrit of 60. This is an increase in the blood corpuscular volume of about 100 % compared with normal values. The plasma volume shows normal values in men, and a small decrease in women.

Following the treatment with radioactive phosphorus the blood corpuscular volume usually decreases in the course of 3—6 months, though only seldom to normal values. In some patients the effect lasts several years, while in others the blood corpuscular volume rises again during the following months. In a few cases no effect on the blood corpuscular volume could be observed and no improvement neither objective or subjective was seen, even though repeated doses of radioactive phosphorus were given.

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FREEDOM AND WELFARE

These three words summarize the belief of the Northern peoples that freedom *and* welfare are but two sides of *one* great movement, the striving of the common man to obtain for himself and his fellows a more satisfying, healthful and secure life. The crucial question is *how* to obtain harmony between the pursuit of such welfare along lines of organizational and governmental action and the love of freedom, that freedom which is essential to enjoying the benefits of welfare, just as security obtained by economic, social and medical welfare is fundamental to practising many essential human freedoms.

The above heading serves as the title of a 500 page book sponsored by the Ministries of Social Affairs of Denmark, Finland, Iceland, Norway and Sweden, edited by G e o r g e R. N e l s o n et al. and printed in Copenhagen in 1953. It aims to provide the interested foreigner with a bird's eye view of selected social patterns in the Northern countries as a whole, these being such a closely interrelated group of parlamentary democracies. This survey explains how the Northern peoples try to obtain a fair balance between a fundamental respect of the rights of the individual and a considerable degree of mutual responsibility and solidarity — the goal being a »Home for the People« worth living in for free men and women.

P. B.

W. H. O. ANESTHESIOLOGY TRAINING CENTER IN COPENHAGEN

In November 1949 the *World Health Organization* sent a representative to Copenhagen to find out whether Denmark needed assistance in any field of Medicine. Representatives from the Danish National Health Service and the University of Copenhagen agreed that anesthesia was one of the few fields in which Denmark needed some help from the outside, on account of the long period of isolation during the war. Professor Husfeldt was found both by the Health Service and the University to be the person to take on him the task of outlining an anesthesia school. This kind of postgraduate training was quite a new experience in Danish Medicine. However, when the planning was progressing, it was decided also to invite doctors from other countries, and since the start trainees from all over the world have come to Copenhagen as WHO Fellows.

43 trainees have spent a year each in Copenhagen, 7 from Norway, 6 from Austria, Finland and Switzerland, 3 from Germany, Sweden and Yugoslavia, 2 from Spain and one from Belgium, Greece, Formosa, France, Iceland, Italy and Turkey. From Holland, Italy, Greece and India doctors have visited the center for shorter periods of time. From Denmark 28 trainees have been through the course, 20 for one year, 4 for two years and 4 for three years.

About 30 instructors and consultants from the United Kingdom and the United States, Norway and Sweden have spent some time in Copenhagen giving lectures and supervising the clinical work. Dr. Ralph Waters and Dr. Stuart Cullen did the pioneer work when the courses were started in May 1950, Dr. Dripps and his associates from Philadelphia have spent varying lengths of time at the Center and from England a number of outstanding anesthetists (Organe, Mushim, Pask, Gillies among others) have been in Copenhagen once or several times. The Danish instructors, ten in number, have benefited much from these visits, and it is hoped that Denmark will be able to train its own anesthetists without help in a few years. Since the Center is now so well established in Copenhagen it may even be wise to invite trainees from other countries also in the future.

The Center was inaugurated on May 1, 1950 and the fourth course is now approaching its end. Prof. Husfeldt has been the director and Dr. Wainø Andersen has acted as the secretary of the school.

Information about previous trainees from Copenhagen is not very detailed as yet, but it is known that out of the 22 foreign trainees of the first two years 8 are in leading positions in their home country. Of the Danish trainees 9 are in leading positions, while the rest are preparing themselves for the specialist recognition, which in Denmark takes at least 6 years after graduation and includes training in Medicine and Surgery.

The clinical training has been carried out in all the larger hospitals of Copenhagen, the University Hospital, the three Municipal Hospitals, the Copenhagen County Hospital, the Finsen Institute and the Orthopedic Hospital. The trainees have rotated between the different hospitals and have participated in the daily routine work under supervision of the visiting and the Danish intructors. The theoretical training has included lectures on a great varity of topics, and special intruction has been given in such subjects as anesthesia in chest surgery and in pediatric surgery, treatment of barbiturate poisoning, anesthesiological problems connected with electro-shock therapy, etc.

All teaching is done in English, and it is no wonder that some of the trainees have language difficulties in the beginning, the more so since trainees from countries other than the Scandinavian have no possibility of talking to most of the patients. This makes adequate bedside teaching a little difficult, but the trainees seem to pick up a good deal of Danish during their stay, and they are well accepted by the Danish patients.

The Center in Copenhagen was the first major project in anesthesia supported by the WHO. Due to the encouraging results from the first courses similar centers have been established in France and Yugoslavia. The aim is to make a nucleus of trainees in each country, around which this important branch of Medicine might develop. And Denmark, so dependant on and interested in exchange with other countries, is happy to be the host of the first center.

F. F.